

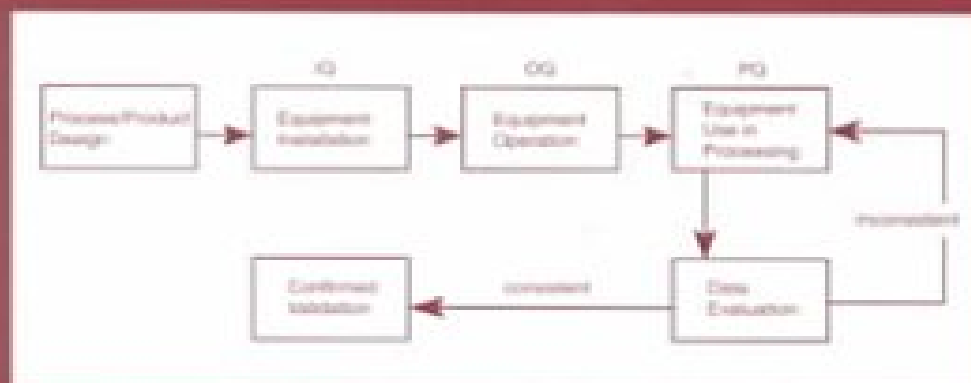
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Good Manufacturing Practices for Pharmaceuticals

A Plan for Total Quality Control
from Manufacturer to Consumer

Fifth Edition, Revised and Expanded



Sidney H. Willig

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**A Plan for Total Quality Control
from Manufacturer to Consumer**

Fifth Edition, Revised and Expanded

Sidney H. Willig
*Temple University
Philadelphia, Pennsylvania*



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Preface

Partisan bickering in the Congress of the United States, with added hostility between the President and the legislature, has occasioned much news media attention in 1999. So, in the United States, as in Europe and Japan, there continues growing political appeal in pressing drug manufacturers for price concessions in response to the problem of funding national health care systems. This has added to consideration of the economy of drugs, biologicals, vaccines, and medical devices; a lesser tolerance for growth in research costs; and a greater demand for reduction in manufacturing outlay. Much healthy innovation in Current Good Manufacturing Practices (CGMPs) will occur, but at some risk. Media criticism of promotional expenses can be anticipated.

Because this edition continues insights requisite to the multinational activities of most manufacturers today, we take note of scientific and legal factors to a greater extent than before. The text contains guidelines that address these factors and questions that the reader will want to analyze in detail and update. We urge our readers to be alert to millennial revisions, additions, and deletions to published standards on which they presently rely. For example, in USP24-NF19, there have been more than 3900 revisions.

The audience for this book is broader than just those involved in the manufacture of pharmaceuticals. This is an invaluable resource for private and independent inspection personnel, local and state inspection agencies, and quality assurance organizations contracted by distributors, and reflects the growing role of

pharmacists acting as employees, or independently, in some aspect of quality control.

With these caveats in place, the efforts, responsibilities, and commitments of governmental authorities and private industry will continue to focus on maintaining CGMPs for pharmaceuticals.

A drug or device shall be deemed to be adulterated—(a)(2)(b) if it is a drug and the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this Act as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess. (21 USC 351)

As experience with federal courts in the United States has indicated, the CGMP regulations are usually held to be substantive and have been used to support the strictest of sanctions by their breach. These regulations truly apply to all drugs, whether or not they are characterized as old drugs; new drugs; Abbreviated New Drug Application (ANDA) drugs; investigational drugs; or ingredients of drugs, devices, or cosmetics. Since the inception of these regulations, if the FDA can establish that the regulatee has not conformed to CGMPs in its procedures, the FDA can allege that the resultant products are adulterated, whether or not they are currently distributed nationally or abroad. Then it may invoke all of its remedies as feasible against the product itself, as well as against the parties responsible, whether corporate or individual, national or extranational.

Current Good Manufacturing Practices have taken on new significance in this era of multinational suppliers of pharmaceuticals. Cross-licensing, joint ventures, strategic alliances, mergers, acquisitions, and divestitures underscore the necessity of maintaining standards of manufacturing and quality control across the geographical boundary of suppliers and distributors. In this edition, we offer enhanced definition of these activities.

Advances in the design of pharmaceuticals, to at once expand and make more specific their applicability to modern medical armamentaria, have added complexities to the entire production process, on through to packaging and storage. Added to this are the growing concerns of adulteration and misbranding, given the potency of many new products.

As if sheer medical and scientific progress were not enough to spur greater concern over CGMPs, new regulatory stress and the impact of legislation have enhanced the responsibilities of manufacturers and other suppliers. New regulatory enforcement, carrying stiff penalties, has been established.

Where other regulated materials have cast a particular light on quality control needs of the distributor by court decisions or legislative or administrative action, they have been noted in this edition.

Hand in hand with this are new enforcement alternatives via the statutory scheme, which threaten imposition of criminal sanctions on wrongdoers. To this end, there has been increased enlistment and training of government regulatory investigators.

The fifth edition of *Good Manufacturing Practices for Pharmaceuticals* both expands on and compresses the considerable material used in composing prior editions. As such, and because of their number, it becomes more difficult to identify contributors. Suffice it to say that the excellent advice of prior coauthors such as Drs. Murray M. Tuckerman, William S. Hitchings IV, and James R. Stoker has been enriched by years of cumulative experience and regulatory interaction. This edition also reflects the cooperation of many private, industrial, and governmental employees on all levels and, where possible, citations have been offered for reference. Among those I would especially note and thank for their courtesy, comments, and assistance are James Ruger, Ph.D., J.D.; Kenneth C.H. Willig, Ph.D, J.D.; and Randi Cane.

Sidney H. Willig

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Introduction

Since the fourth edition of this book appeared, there have been major changes in the governmental agencies, such as the FDA in the United States, as well as in the manufacturing industry, where much realignment has taken place. These changes, along with the fluctuation in the economics of global markets on which the industry depends, have created new methods of self-governance.

The introduction of the Pre-Approval Inspection procedure linked product registration approval to Current Good Manufacturing Practice (CGMP) compliance. Delays in approvals have an adverse impact on the public as well as on pharmaceutical manufacturers, and media notice has pressured the FDA.

The increased autonomy of FDA district offices has sometimes created less than consistent interpretation and application of the regulations. This has been exacerbated by the FDA's aggressive use of extensive inspections (especially in the United States) and its issuance of large numbers of 483s, warning letters, and consent decrees. Some effort to improve internally has been made by compliance policy guides made available to each district office. Some companies have left themselves vulnerable by their inadequate attention to compliance.

As many of our readers are aware, the FDA explains its policy on regulatory issues related to its statutory and regulatory authority in various ways. Using materials that have recently become available, we have tried to reflect these positions for your information. One such method consists of the series of compliance policy guides provided to field inspection and compliance staffs, regarding FDA

standards and procedures for determining compliance with Current Good Manufacturing Practice regulations. In this edition, we have sought to integrate and identify the pertinent guides wherever applicable in the text, rather than simply rely on our chapters dealing with inspection, which afford a broader vision of inspection for the regulatee's preparation. It is our hope that using this additional method will reinforce the regulatee's attention to both substance and procedure involved in FDA and equivalent national and international inspections.

There has been increased emphasis on the application of CGMPs to the manufacturer of bulk pharmaceutical chemicals, and a separate chapter has been included on this subject.

There has been some impact, mainly positive, from the International Conference on Harmonization, representing Europe, Japan, and the United States. Agreed-upon standards now exist for analytical method validation and for stability and impurities in new products. General agreement on product/production change requirements and on GMPs would be particularly valuable since the industry is now global. However, owing to difficulties in obtaining agreement among the parties, progress is unlikely. A chapter has been included to highlight key issues and differences among GMPs of Europe, Canada, and the World Health Organization (WHO).

As with previous editions, we have tried to provide some practicality to the application and understanding of the regulations. Several FDA guides and guidelines have been issued or updated in recent years, but the CGMP regulations have undergone only isolated changes, and they are now in need of an overhaul. It is hoped that this might be a collaborative project involving both the FDA and the industry, especially on a global scale. The FDA publishes guidelines and proposed regulatory changes in the *Federal Register*, thereby providing opportunities for comment. However, interactive involvement to discuss issues would help to prevent later confrontation without detracting from the FDA's responsibilities. At one time, compliance with an FDA guideline, while not mandatory, was considered compliance with the relevant section of the CGMP regulations. However, FDA lawyers have since stated that it is inappropriate to have interpretive documents that are binding only on one party (the FDA). Consequently, adherence to a guideline is no longer an assurance of CGMP compliance. (See Chapter 1 *infra*.) This constitutes a fundamental difference from other GMPs, in which following the entire GMP document as a guideline constitutes compliance, even while alternative approaches remain acceptable.

The increasing use of inspection guides by the FDA to provide interpretation of the regulations bypasses the review process, since these are considered to be internal documents.

It is a worthwhile and necessary addition to the framework of each manufacturing company to establish a written CGMP compliance program for each facility, along with a reasonable calendar for review and update. That is, of

course, only one portion of the job. Unless that responsibility is undertaken to be implemented in a timely and conscientious manner, product failures attributable to errors in the established process will result in enforcement activity and remedial litigation. Therefore, the confidential conduct of internal investigation and audit must be accompanied by a willingness to report circumstances that denote insufficient care and even misconduct. And the organization must respect the need to address problems promptly and fully, whether or not enforcement by authorities is imminent or threatened.

Many of these procedures must utilize the effort and initiative of the organization's managers, executives, and professionals. In my long-term pharmaceutical experience, whether or not consultants are used, the role of company counsel in explaining self-evaluative privileges along with attorney-client and work-product protection is essential.

Depending on the spectrum of company activity, compliance programs must embrace a variety of sales, distribution, antitrust, labor, employment, and environmental issues.

More than ever, many of our contributors have emphasized that the global nature of the pharmaceutical industry and its collateral and supportive industries has created the need for geographical distribution of manufacturing facilities, accommodation to a diversity of regulatory and statutory governance, and adaptation to disparate human resources. In this new environment, cultural differences must be appreciated. The multinational manufacturer whose major roots lie outside the United States may not comprehend the strong reliance in the United States on litigation as a means of resolving matters that range from employment discontent to regulatory enforcement and even commercial disputes. Our European and Asian colleagues, who are accustomed to resolving conflicts via nonjudicial processes or within legal systems that operate quite differently from ours, can find the U.S. style of interplay somewhat bewildering.

Similarly, the multinational manufacturer whose major base is in the United States may often be frustrated by difficulties in attempting redress from suppliers and vendors who are sheltered by unique legal insulation in their country of origin. Often, despite the use of scientific, regulatory, and legal consultants conversant with special geographic areas, one finds that attitudes, traditions, and legal resources of the extranational area intransigent to the types of remediation found in the United States.

Acquisitions, mergers, and downsizing in recent years have been consistent in the industry. For the United States-based manufacturer, not only has this resulted in a diminution of manufacturing facilities and transference of operations abroad, but it has also led to a revolution in the innovation of labor-soaring equipment. Beyond the care required for the introduction of such equipment, reductions in the workforce are a fertile source of employment litigation and enforcement initiatives.

There is a great need in most major producing nations, such as the United States, to be aware of federal, state, and even local plant closing laws, and the assembled antidiscrimination statutes that may be invoked. Overworked and dissatisfied employees are a potential source of internal strife, and, along with released employees, provide regional and even national agencies with complaints that encourage investigative follow-up. In some national forums, particular emphasis is placed on sexual harassment and the multinational must be sensitive to specific litigatory concerns in the province of operation.

My fundamental advice is for a current good manufacturing system that comprises those who “do” and those who independently audit the “doing.” Systems that become so employee-depleted that these functions cannot remain separate and independent are under an obvious handicap.

GMPs, although important, represent only one element in maintaining and improving quality. If product quality is defined as meeting or exceeding customer needs and expectations, then mere compliance with GMPs does not provide assurance of meeting these requirements. GMP compliance is essentially a bureaucratic exercise, but one designed to improve quality, consistency, product safety, and efficacy. Other approaches are being used to drive the progress of quality with respect to customer satisfaction and the resulting business success. A new chapter has been included in this edition to describe two of these approaches: the Malcolm Baldrige National Quality Award and ISO 9000.

The health care industry will continue to be regulated with a quality of judgment and reason that is exhibited in the main. We hope and anticipate that in the future the parties involved will be working cooperatively for the mutual benefit of all—the customers, the industry, and the public.

Status and Applicability of U.S. Regulations

Current Good Manufacturing Practices in Manufacturing, Processing, Packaging, and Holding of Drugs

This chapter addresses FDA and some other federal regulations that have been promulgated for statutory effectuation and implementation in the main. The major statute underlying such regulations is the Federal Food, Drug and Cosmetic Act as amended, which may be found in the U.S. Code at 21 USC 321 through 392.

The regulations discussed in the main are found at Title 21 of the Code of Federal Regulations. The latter is composed of nine volumes. The parts in these volumes are arranged in the following order: Parts 1–99, 100–169, 170–199, 200–299 (containing the bulk of the CGMPs), 300–499 (containing the bulk of the IND, NDA, and ANDA materials), 500–599, 600–799, 800–1299, and 1300–end. This last volume addresses matters subject to Drug Enforcement Administration (DEA), the Department of Justice (DOJ), and the Office of National Drug Control Policy.

The text also addresses guidelines, recommendations, and agreements that for the most part are governmental in derivation. A new addition to the Appendix herein provides the official definitions for such and at the same time provides clues as to the reliance manufacturers may attach to a guideline, a recommendation, or even formal agreements and memoranda of understanding or other similar written documents executed by the FDA (21 CFR 10.90 et seq.).

Similarly, the FDA has carefully defined the term Advisory Opinion at 21 CFR 10.85 and—of special importance in the context of Chapter 18 following

dealing with inspective concerns of both “inspecteds” and “inspectors”—a statement made or advice by an FDA employee is not an advisory opinion unless issued in writing under that part. Where the assurance or advice is given orally, it is regarded as an informal communication that represents the personal best judgment of that employee, not the FDA, and does not obligate the agency or commit it to the views expressed.

Current Good Manufacturing Practices (CGMP) regulations (21 CFR 210–226) are promulgated by the Commissioner of the Federal Food and Drug Administration (FDA) under Section 701(a) of the Federal Food, Drug and Cosmetic Act [21 USC 371(a)] in furtherance of the requirement of Section 501(a)(2)(B) of the Act [21 USC 351(a)(2)(B)], which specifies that a drug is deemed adulterated “if the methods used in, or the facilities or the controls used for, its manufacture, processing, packing or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice.” The purpose of Section 501(a)(2)(B) is to assure that such drug meets the requirements of the act as to safety and has the identity and strength and meets the quality and purity characteristics which it purports or is represented to possess. The FDA is of course committed to various programs and systems designed to assure the quality of all drug products by careful monitoring of drug manufacturer’s compliance with CGMP regulations. In order to identify their regulatees, Section 510(b) and (c) of the FFDC Act requires the registration of all producers of drugs and devices. Congressional language that accompanied this amendment stated it was “necessary to provide for the registration and inspection of all establishments in which drugs were manufactured, prepared, propagated, compounded or processed” since these products were likely to enter interstate commerce. Section 510(h) requires that each registrant be inspected for compliance every two years.

The FDA includes as registrants manufacturers whose final products are homeopathic drugs and requires that such products must be manufactured in conformance with CGMPs but some requirements of 21 CFR 211 are considered by them to be inapplicable. We have included FDA Compliance Guides as to preparation for, and marketing of, homeopathic drugs, below.

The approval process for drug marketing applications (original and abbreviated new drug applications and Antibiotic Forms 5 and 6) includes a review of the manufacturer’s compliance with the CGMPs.

In recent years the FDA has assumed additional roles for assurance to vendees through programs like the Government-Wide Quality Assurance Programs for drug purchase contracts by the Department of Defense and Veterans Affairs and the MAC program (Maximum Allowable Cost) program that became seminal to the manufacture of generics.

Decisions regarding compliance with CGMP regulations are based on inspection of the facilities, sample analysis, and compliance history of the firm.

These data are summarized in profiles that represent several years of history of the firms.

CGMP deficiencies supporting regulatory action by the FDA also support decisions regarding nonapproval of NDA Supplements, as well as the purchasing contracts and candidacy for MAC, so some FDA expanded action is likely. Therefore, issuance of a “warning” letter or other regulatory action based on discovery of CGMP deficiencies must be accompanied by disapproval of any pending NDA, ANDA, or Supplement, or any government contract produced under the same deficiencies.

The Federal Food, Drug and Cosmetic Act applies to drugs introduced into interstate commerce in the United States, including drugs exported to or imported from other countries. Manufacturers in other countries who export to the United States are inspected either by the FDA or under reciprocal inspection agreements as part of the New Drug Application (NDA) approval process and antibiotic drug certification. Currently, such agreements exist between the United States and Sweden, Switzerland, and Canada. Individual drug products are subjected to extensive examination, including laboratory testing, before being allowed into the United States.

The FDA has the authority to deny entry to any drug, if there is a question regarding its safety, identity, strength, quality, or purity. This authority is exercised unless factory inspection is permitted or inspection information is available concerning nondomestic firms, in lieu of conducting foreign inspections. Although this authority is exercised more rarely and tempered by Chapter 8 of the Act, the FDA also has the authority to deny exit to questionable drugs. (See also Chapters 23 and 24 in this volume.)

The plan proposed by the authors is not designed as a minimum or as a regulatory compliance program, but as a viable approach that seeks to ensure the quality of pharmaceutical preparations. It has a sound economic base in that at every step of its preparation the question was asked: “If this is not done, aside from susceptibility to legal actions, what are the probable economic consequences?” If the consequences are potentially more costly than the use of the indicated control, the control is recommended. Built into the system are such factors as quality control, security, personnel evaluation, and the inevitable documentation trail of paper to show what was done, who did it and when, and who saw and attested to the doing.

The problem is approached from the perspective of a consultant who has a free hand to suggest procedures. Recommendations are presented primarily as checklists covering aspects of quality control. Some areas of concern are indicated without recommendations as specific control procedures.

The Food and Drug Administration strives to ensure that the regulated industries comply with a total quality control concept through its factory inspection

programs and through participation in voluntary CGMP compliance seminars and workshops sponsored jointly with the industries or with educational institutions. The fact that a total quality control approach is necessary to prevent a drug product from being deemed adulterated under Section 501(a)(2)(B) and violative of Section 301(b) of the Food, Drug and Cosmetic Act is indicated by 21 CFR 211, Current Good Manufacturing Practice for Finished Pharmaceuticals. Nowhere in government documents or official compendia, however, is there a comprehensive collection of specific measures to realize this concept. The concept of a total quality control system is neither limited in scope to the analytical methods of assay, control charts, product inspections made during the manufacturing processes and prior to finished dosage form distribution, nor to the statistical techniques utilized in these discrete operations. The concept includes all control measures contributing to the completed market dosage form. The Pharmaceutical Manufacturers Association in its "General Principles of Total Control of Quality in the Drug Industry" consistently has stated that "Total control of quality as it applies to the drug industry is the organized effort within an entire establishment to design, produce, maintain and assure the specific quality in each unit or drug distributed. Total control of quality is a plant-wide activity and represents the aggregate responsibility of all segments of a company."

In the following chapters an attempt is made to provide specific guidelines and concepts that can serve as checks for critical operations within the entire organization in order that a total quality control system can be achieved. Each requirement that is loosely generalized in Good Manufacturing Practice regulations will be enlarged and made more specific in order to include measures that the authors believe are necessary for good control.

§210.1 STATUS OF CURRENT GOOD MANUFACTURING PRACTICE REGULATIONS

(a) The regulations set forth in this part and in Parts 211 through 229 of this chapter contain the minimum current good manufacturing practice for methods to be used in, and the facilities or controls to be used for, the manufacture, processing, packing, or holding of a drug to assure that such drug meets the requirements of the act as to safety, and has the identity and strength and meets the quality and purity characteristics that it purports or is represented to possess.

(b) The failure to comply with any regulation set forth in this part and in Parts 211 through 229 of this chapter in the manufacture, processing, packing or holding of a drug shall render such drug to be adulterated under section 501(a)(2)(B) of the act and such drug, as well as the person who is responsible for the failure to comply, shall be subject to regulatory action.

§210.2 APPLICABILITY OF CURRENT GOOD MANUFACTURING PRACTICE REGULATIONS

(a) The regulations in this part and in Parts 211 through 229 of this chapter as they may pertain to a drug and in Parts 600 through 680 of this chapter as they may pertain to a biological product for human use, shall be considered to supplement, not supersede, each other, unless the regulations explicitly provide otherwise. In the event that it is impossible to comply with all applicable regulations in these parts, the regulations specifically applicable to the drug in question shall supersede the more general.

(b) If a person engages in only some operations subject to the regulations in this part and in Parts 211 through 226 and Parts 600 through 680 of this chapter, and not in others, that person need only comply with those regulations applicable to the operations in which he or she is engaged. (See also 21 CFR 207.)

§210.3 DEFINITIONS

(a) The definitions and interpretations contained in section 201 of the act shall be applicable to such terms when used in this part and in Parts 211 through 226 of this chapter.

(b) The following definitions of terms apply to this part and to Parts 211 through 226 of this chapter.

(1) “Act” means the Federal Food, Drug, and Cosmetic Act, as amended (21 USC 321, et seq.).

As described in the *Federal Register*, this general introduction to what is projected as a series of Good Manufacturing Practice (GMP) regulations for all human drug products, as well as specific products or specific processes, is “intended to be general enough to be suitable for essentially all drug products, flexible enough to allow the use of sound judgment and permit innovation, and explicit enough to provide a clear understanding of what is required.” The concept places a large burden on the manufacturer of pharmaceuticals. Adherence to the explicit regulations is a required minimum, but it is not adequate to ensure that a manufacturer is in compliance. In addition, the manufacture of a pharmaceutical must be by current methods with current controls, thus setting as a requirement that which is current or generally accepted in the drug industry as appropriate equipment, methodology, controls, and records. Even being “average” in all respects, compared with the industry, does not ensure that a manufacturer is in compliance, because the standard is not only that practices be “current” but that they also be “good.” Thus, if a new practice is introduced anywhere in the industry that is better than what is current, then all manufacturers may seem obligated to adopt the better practice.

Therefore, it can be seen that being in compliance with GMP is not a static situation, but requires the manufacturer to be aware not only of what is current in the industry but also to be aware of innovations that may be good. It would seem also that a legitimate inquiry for evaluation of compliance is the measures taken by a manufacturer to obtain knowledge, on a continuing basis, of both what is current and may be good and to provide a method for incorporating the necessary changes into the already established system of manufacture and control.

The FDA currently makes available in electronic format various analytic data from its centers. Those who do analytic work for manufacturers should be certain they are optimizing their knowledge of such accessible data by inquiry of the FDA, their own association resources, and that of the Association of Food and Drug Officials of the United States. Sometimes these additional resources are also noted at FDA Science Forums on the Regulatory Sciences, and abstracts may be available. For example, information routinely maintained within the Division of Pesticides and Industrial Chemicals can be retrieved. These data are accessible via the Prime Connection electronic bulletin board of the Center for Food Safety and Applied Nutrition (CFSAN), accessible via an 800 number to anyone with a computer and modem, and CFSAN's VAX computer anonymous file transfer protocol (FTP) site, accessible via the Internet.

There is a current menu as to other sources of information from and about the FDA that will aid regulatees at the end of this chapter.

USP Reference Standards are highly characterized specimens of drug substances, major impurities, degradation products, and performance calibrators for use in testing drugs and nutritional supplements. They are used to perform official methods of analysis in pharmaceutical testing. The manufacturer may use other than the official method of analysis, but on FDA inspection and challenge, the substance used and the product manufactured must meet the official specifications contained in the USP-NF following the official method of analysis. USP Material Safety Data Sheets are available to purchasers of standards. USP also tests and distributes other authenticated substances not currently included in the USP-NF that are still in sufficient demand; FCC Reference Standards specified in the latest edition of the Food Chemicals Codex; and highly purified samples of chemicals, including drugs of abuse. Readers who seek information as to specific USP Reference Standards, whether or not current, can call 1-800-227-8772 in the United States or 1-301-881-0666 for outside the U.S. and Canada.

It goes without saying that constant update acquisition of official and unofficial compendia is necessary for timely attention to the CGMPs as well. The law requires that products meet the requirements of the United States Pharmacopeia (USP)/National Formulary for the monographs applicable to their products as labeled. Since these are not static, good reasoning, good science, and good practical issues arise. (See Appendix E below.) For example, where the manufacturer has prepared the product in accord with the pertinent USP monograph and

that monograph undergoes a significant change five years later as to its methodology of analytic controls, what is a reasonable approach for the manufacturer? First, the manufacturer should implement the new controls promptly. As to product samples held in reserve, they are examples of product legally placed into Interstate Commerce under analytic controls then in effect, and any obligation to retest them might not be reasonable. The exception might rest on the nature and importance of the change to such a product and on whether the manufacturer might have knowledge that the former method would find the product out of control in the marketplace at this date. In such an instance the safety and effectiveness of the product would weigh upon any decision. I am advised by Lee T. Grady, Ph.D., that in preparing USP24-NF19 there have been 3900-plus revisions. See a listing below.

Some troublesome questions that might arise are: When is a piece of machinery no longer in compliance? For example, now that encapsulators are available that can fill to a relative standard deviation of not more than 6%, is the use of old equipment that has a relative standard deviation of about 8% a violation per se? What about the use of fully automated tablet presses with a relative standard deviation for tablet weights of about one-half that of the conventional presses? Should molded tablets with their very high (approximately 10%) relative standard deviation for weight be permitted, when small, compressed tablets can be produced with a relative standard deviation of about 4%?

It would seem that the answers to these questions are a matter of judgment, depending on the drug involved, official or NDA monographs, and other factors. The judgment will be that of the manufacturer, whose label claims must be completely truthful, but the foundation for continuing dialogue between the FDA and industry, if not controversy, has been laid.

The Congress intended that the phrase itself (current good manufacturing practice) have a unique meaning. . . . The agency determines what constitutes "current good manufacturing practice" based upon its experience with the manufacture of drugs through inspectional and compliance activities. . . . Although the practices must be "current" in the industry, they need not be widely prevalent. Congress did not require that a majority or any other percentage of manufacturers already be following the . . . practice . . . that . . . had been shown to be both feasible and valuable in assuring drug quality.
[*Federal Register*]

The FDA also holds that, although it does not manufacture drugs, it has the unique ability to determine Current Good Manufacturing Practices for drugs, since it alone has access to the facilities and records of every manufacturer of pharmaceuticals in the United States. Given the fact that many processes and controls are considered by individual manufacturers to be trade secrets, competitors, through the various associations of manufacturers or independent third par-

ties, such as the compendial authorities, are not likely to discover what nonpublic practices are current.

Even if current practices were available, the FDA holds that it has special technical and scientific expertise to determine which of the current practices are also good. This expertise is inherent in reviews of production and control techniques in New Drug Applications and Abbreviated New Drug Applications (ANDAs), supplemental applications, antibiotic certification forms, biological establishment and product licenses, new animal drug applications, and proposed and final compendial standards. Additional experience is based on establishment inspection reports filed by FDA investigators and the monitoring of drug recalls.

A current, although not necessarily predominant, practice is considered “good” if:

1. It is feasible for manufacturers to implement.
2. It contributes to ensuring the safety, quality, or purity of the drug product.
3. The value of the contributions or added assurance exceeds the cost in money or other burdens of implementing or continuing the practice.

Also, note that in addition to proceeding against the drug, regulatory action may be taken against the person who is responsible for the failure to comply. Responsibility for failure to comply would seem extensible vertically from management, which did not supply adequate supervision or directions, through quality control and individual production people, who did not follow directions, and horizontally to supplies of raw materials, whose products did not meet purported specifications, as well as to contract laboratories. Since criminal penalties (fines and/or prison sentences) are possible, these regulations impose a standard of responsibility to have knowledge, to train subordinates, and to continually check to ensure compliance with directives.

The legal standard for responsibility for all those engaged in drug manufacture is high. People entering this field of endeavor should be aware of the special burden of complete accountability. Violation of the Federal Food, Drug and Cosmetic Act is handled under unique legal doctrine that does not require proof of criminal intent as a prerequisite for criminal culpability. In order to provide maximum protection of the public health, Congress purposely neither required that actual harm from contamination of a drug product has to be proven for a charge that the product is adulterated nor that each article in the batch be adulterated before the entire amount is subject to condemnation or other action. The law is aimed not only at removal of the adulterated article from commerce, but for the same offense, and simultaneously, may seek punishment of a person. Note the “person” is defined in Section 201(e) of the act to include corporations and partnerships, as well as individuals. Landmark judicial decisions are (1) *United*

States v. Dotterweich, 320 U.S. 277 (1943) and (2) *United States v. Park*, 421 U.S. 658 (1975).

Almost all civil and criminal actions initiated by the FDA are derived from violations of statutory definitions of misbranding and adulteration. This fact is magnified by both the expanded areas of definition and prohibitions created by the New Drug Amendments and the prevalent judicial policy of liberal construction of the statute with its prime objective of consumer protection.

Currently, the adulteration statute, aside from the regulations on Good Manufacturing Practices, holds that the presence of a foreign substance, even of distinct and contrary appearance from the product itself, could cause it to be adulterated. Previously, distinct substances, such as nails or pieces of a container not commingled in such a manner as to masquerade as a part of the food itself, would not have been considered an ingredient in support of a charge of adulteration. However, the courts have not been entirely consistent as to this interpretation, and no doubt the subject regulations will be used to strengthen the FDA position of greater inclusion.

In 1952, a landmark decision in the 8th Circuit stated that a defendant might enjoy a certain latitude where a "mere possibility" of contamination existed, subject to proof that factory conditions "would with reasonable possibility result in contamination" (*Berger v. The United States*, 200 F.2d 818). Obviously then, today's Good Manufacturing Practice regulations are viewed as the means for the FDA to present to the court this "reasonable possibility" based on breach of said regulations. To increase the chances of success for enforcement, evidence from examination of samples will frequently be offered to show that the possibility is realized.

(2) "Batch" means a specific quantity of a drug or other material that is intended to have uniform character and quality, within specified limits, and is produced according to a single manufacturing order during the same cycle of manufacture.

(3) "Component" means any ingredient intended for use in the manufacture of a drug product, including those that may not appear in such drug product.

(4) "Drug product" means a finished dosage form, for example, tablet, capsule, solution, etc., that contains an active drug ingredient generally, but not necessarily, in association with inactive ingredients. The term also includes a finished dosage form that does not contain an active ingredient but is intended to be used as a placebo.

(5) "Fiber" means any particulate contaminant with a length at least three times greater than its width.

(6) "Non-fiber-releasing filter" means any filter, which after any appropriate pretreatment such as washing or flushing, will not release fibers into the component or drug product that is being filtered. All filters composed of asbestos are deemed to be fiber-releasing filters.

(7) "Active ingredient" means any component that is intended to furnish

pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure of any function of the body of man or other animals. The term includes those components that may undergo chemical change in the manufacture of the drug product in a modified form intended to furnish the specified activity or effect.

(8) “Inactive ingredient” means any component other than an “active ingredient.”

(9) “In-process material” means any material fabricated, compounded, blended, or derived by chemical reaction that is produced for, and used in, the preparation of the drug product.

(10) “Lot” means a batch, or a specific identified portion of a batch, having uniform character and quality within specified limits; or, in the case of a drug product produced by continuous process, it is a specific identified amount produced in a unit of time or quantity in a manner that assures its having uniform character and quality within specified limits.

(11) “Lot number, control number, or batch number” means any distinctive combination of letters, numbers or symbols, or any combination of them, from which the complete history of the manufacture, processing, packing, holding and distribution of a batch or lot of drug product or other material can be determined.

(12) “Manufacture, processing, packing, or holding of a drug product” includes packaging and labeling operations, testing and quality control of drug products.

(13) “Medicated feed” means any “complete feed,” “feed supplement,” or “feed concentrate” as defined in § 558.3 of this chapter and is a feed that contains one or more drugs as defined in section 201 (g) of the act. Medicated feeds are subject to Part 225 of this chapter.

(14) “Medicated premix” means a substance that meets the definition in § 558.3 of this chapter for a “feed premix,” except that it contains one or more drugs as defined in section 201 (g) of the act and is intended for manufacturing use in the production of a medicated feed. Medicated premixes are subject to Part 226 of this chapter.

(15) “Quality control unit” means any person or organizational element designated by the firm to be responsible for the duties relating to quality control.

(16) “Strength” means:

(i) The concentration of the drug substance (for example, weight/weight, weight/volume, or unit dose/volume basis), and/or

(ii) The potency, that is, the therapeutic activity of the drug product as indicated by appropriate laboratory tests or by adequately developed and controlled clinical data (expressed, for example, in terms of units by reference to a standard).

(17) “Theoretical yield” means the quantity that would be produced at any appropriate phase of manufacture, processing, or packing of a particular drug product, based upon the quantity of components to be used, in the absence of any loss or error in actual production.

(18) “Actual yield” means the quantity that is actually produced at any ap-

propriate phase of manufacture, processing, or packing of a particular drug product.

(19) “Percentage of theoretical yield” means the ratio of the actual yield (at any appropriate phase of manufacture, processing, or packing of a particular drug product) to the theoretical yield (at the same phase), stated as a percentage.

(20) “Acceptance criteria” means the product specifications and acceptance/rejection criteria, such as acceptable quality level and unacceptable quality level, with an associated sampling plan, that are necessary for making a decision to accept or reject a lot or batch (or any other convenient subgroups of manufactured units).

(21) “Representative sample” means a sample that consists of a number of units that are drawn based on rational criteria such as random sampling and intended to assure that the sample accurately portrays the material being sampled.

The role of the United States Pharmacopeia is of course not limited to the United States. This was true even prior to the time it became incorporated within the Federal Food, Drug and Cosmetic Act, for its ultimate importance in dealing with such portions of that law that recite prohibited acts. There are other pharmacopeia with substantial recognition in the global and local manufacture and distribution of pharmaceuticals, but the U.S. Pharmacopeia is a major reference in this regard.

For that reason, and for the fact that in 1999 the USP announced a major structural reorganization for improved focus responsive to the “ongoing transformation of health care science and technology,” it is perhaps helpful to briefly review its historic and present important role in the manufacture, labeling, and standard setting vital to pharmaceutical manufacture.

Established in 1820 “to ensure that consumers receive medicines of the highest possible quality, strength and purity in the United States,” it was destined to reflect medical and pharmaceutical advances from the major European laboratories and academia from the first. At present the USP provides standards for more than 3,400 drugs and dosage forms for medicines and dietary supplements.

While it has taken on additional duties in the areas of reporting and prevention programs regarding product problems and medication errors, the interest of our readers is better expressed within their traditional roles in standard setting.

These can be summarized (and are currently handled by a newly formed division following the 1999 reorganization) as follows:

Standards—General Policies, Requirements, Nomenclature and Labeling, Veterinary Drugs, Excipients/Pharmaceutical Waters, Biologics and Biotechnology, Dietary Supplements, and Pharmaceuticals, which also includes the Reference Standards Laboratory and the Research and Development Laboratory.

Located nearby the FDA in Rockville, MD 20852, they can be reached at 301-998-6821, www.usp.org.

Under Uniform State Food and Drug Laws, the Federal Food, Drug and Cosmetic Act, and the recent Food and Drug Administration Modernization Act, USP-NF standards are legally enforceable.

These standards are published in the USP-NF and legally recognized. And once the Food and Drug Administration approves a new drug product, the USP establishes public standards for same that become similarly enforceable. It is hard to imagine that a manufacturer would not have copies of the current USP24/NF19 compendium available to the staff. All proposed revisions to USP-NF standards are published for review and comment in a USP publication, *Pharmacopeia Forum*. The USP-NF is, of course, also available on CD-Rom.

In this text we are advising you to check carefully information we have provided through the cooperation of USP staff members concerning the titles of all test standards that the USP has added, revised, or deleted for the latest edition. For manufacturers and others, the USP publishes a catalog that contains some prior standards and monographs that are still required from time to time. The USP Reference Standards Catalog contains official lot numbers and pricing information for more than 1,250 established USP Reference Standards used in official USP-NF testing methods for prescription and non-prescription drugs, drugs of abuse, and excipients (see Appendix E below).

Supplemental information available to the reader:
FDA's Electronic Bulletin Board—Available free by computer modem access (dial 1-800-222-0185). Provides the latest information from the FDA, including:

- *FDA Medical Bulletin*
- *FDA Enforcement Report*
- *FDA Consumer* features
- Summaries of *FDA Federal Register* documents
- News releases, talk papers, backgrounders
- Speeches
- FDA congressional testimony

Special Instructions: Set modem to 7 bits, even parity, full duplex, and 1 stop bit. To start, prompts and responses are:

- Login > bbs
- Enter A Topic Code > Manual
- Enter BBS Command > Help

For more information, write Parklawn Computer Center (BBS), 5600 Fishers Lane, Room 2B59, Rockville, MD 20857; or call (301) 443-7318.

FDA Consumer—The official magazine of the FDA. Ten issues a year, each containing in-depth feature articles written for the general public on FDA-related health issues. Also includes reports from FDA's own investigators that go behind the scenes to show how the agency protects the public from unsafe

or worthless products. Subscriptions available for \$15 per year from the Superintendent of Documents, Government Printing Office, Washington, DC 20402-9371.

FDA Medical Bulletin—Information about FDA-related issues and activities of particular interest to health professionals. Sent to more than a million doctors and other health professionals approximately three times a year. Send requests to be placed on the mailing list to FDA Medical Bulletin, Circulation Dept. (HFI-43), 5600 Fishers Lane, Rockville, MD 20857.

FDA Enforcement Report—Weekly update on actions taken in connection with agency regulatory activities, including seizures, injunctions, prosecutions, and dispositions. Recalls and medical device safety alerts voluntarily conducted by firms are also included. Subscriptions are available for \$78 per year from the Superintendent of Documents, Government Printing Office, Washington, DC 20402-9371.

Scientific and Technical Publications—Lists scientific and technical publications written by the Center for Food Safety and Applied Nutrition. Issued annually. Copies are available from the Office of Management, Center for Food Safety and Applied Nutrition, FDA 200 C St., S.W., Washington, DC 20204.

FDA Veterinarian—Published bimonthly, this FDA publication covers current issues concerning animal drugs, food additives, and devices. Subscriptions are available for \$5 per year from the Superintendent of Documents, Government Printing Office, Washington, DC 20402-9371.

Approved Drug Products with Therapeutic Equivalence Evaluations—Commonly called the “Orange Book,” the publication is available for \$91 a year from the Superintendent of Documents, Government Printing Office, Washington, DC 20402-9371. A subscription includes periodic updates of the drug listings.

FDA’s Breast Implant Information Line—Provides up-to-date information on breast implant studies and regulatory status. Call (1-800)532-4440; TTY (1-800)688-6167.

FDA’s Seafood Hotline—Provides information on seafood safety and regulations. Public affairs specialists are available to answer questions from noon to 4 p.m. Eastern time, Monday through Friday. At other times callers can listen to a recording on current seafood topics and leave messages to receive educational material or to report suspected seafood safety problems. Call (1-800)332-4010; (202)205-4314 in the Washington, DC, area.

AIDS Clinical Trial Information Service (ACTIS)—Provides information about AIDS and HIV-related trials currently under way throughout the United States. ACTIS is a joint project of the Centers for Disease Control and Prevention, the National Institutes of Allergy and Infectious Diseases, the National Library of Medicine, and FDA. Call (1-800)TRIALS-A between 9 a.m. and 7 p.m. Eastern time, Monday through Friday.

FDA's CD-ROM—The FDA Office of Information Resource Management has created a CD-ROM containing FDA manuals and documents. This subscription service is updated quarterly and includes easy-to-use search software and a user's guide. Documents currently available include:

- Center for Drug Evaluation and Research, Current Good Manufacturing Practices, and New Drug Applications Guidelines
- Center for Veterinary Medicine policy and procedures
- Chemistry Review
- Code of Federal Regulations (Title 21)
- Compliance Policy Guides
- Drug Study/Health Fraud Bulletins
- FDA Import Alert Retrieval System
- FDA Phone Book
- Food, Drug and Cosmetic Act and Related Laws
- Investigations Operations Manual
- Market Names of Fish
- Medical Products Quality Manual
- New Regulations (Title 21)
- Preamble Medical Devices Reporting Regulations
- Regulatory Procedures Manual, Chapter 5
- Regulatory Procedures Manual, Chapter 8
- Talk Papers/Press Releases

For more information on this service, call FDA's Office of Information Resources Management at (301)443-6770.

ADDITIONAL REFERENCES

Reinventing the Food and Drug Administration—Marie A. Urban: Food, Drug, Cosmetic and Medical Device Law Digest, Vol. 14, No. 2, 5/97.

The Generic Industry: An FDA Insiders View—Gerald F. Meyer: F.D.C.M.L. Digest Vol. 7, No. 2. (May 1990).

Current Developments—FDA Reform. Vol. 14, No. 1 (Jan. 1997).

Following study of this chapter, it might be helpful, for staff review, to discuss specific guides provided by the FDA to their field staff and others that are pertinent as Regulatory Action Guidance.

Sec. 450.100 CGMP Enforcement Policy—OTC vs Rx Drugs (CPG 7132.10)

BACKGROUND:

Because of increased visibility and promotion of certain OTC preparations, there are periodic inquiries from district offices regarding whether or not the enforcement policy for CGMP regulations is the same for OTC drug products as it is for prescription (Rx) drug products.

Section 501(a)(2)(B) of the Federal Food, Drug and Cosmetic Act requires drugs to be manufactured in conformance with current good manufacturing practice. This section does not differentiate between OTC and Rx products and it was not intended by Congress to do so.

A prescription drug may be toxic or have other potential for harm, which requires that it be administered only under the supervision of a licensed practitioner (section 503(b)(1) of the Act). For this reason, problems associated with its manufacture are generally more likely to cause serious problems.

POLICY:

The CGMP regulations apply to all drug products, whether OTC or prescription.

REGULATORY GUIDANCE:

The selection of an enforcement action to be applied will be based on the seriousness of the deviation, including such factors as potential hazard to the consumer.

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2

Finished Pharmaceuticals General Provisions (Subpart A)

§211.1 SCOPE

(a) The regulations in this part contain the minimum current good manufacturing practice for preparation of drug products for administration to humans or animals.

(b) The current good manufacturing practice regulations in this chapter, as they pertain to drug products, and in Parts 600 through 680 of this chapter, as they pertain to biological products for human use, shall be considered to supplement, not supersede, the regulations in this part unless the regulations explicitly provide otherwise. In the event it is impossible to comply with applicable regulations both in this part and in other parts of this chapter or in Parts 600 through 680 of this chapter, the regulation specifically applicable to the drug product in question shall supersede the regulation in this part.

(c) Pending consideration of a proposed exemption, published in the *Federal Register* of September 29, 1978, the requirements in this part shall not be enforced for OTC drug products if the products and all their ingredients are ordinarily marketed and consumed as human foods, and which products may also fall within the legal definition of drugs by virtue of their intended use. Therefore, until further notice, regulations under Part 110 of this chapter, and where applicable, Parts 113 to 129 of this chapter, shall be applied in determining whether these OTC drug products that are also foods are

manufactured, processed, packed, or held under current good manufacturing practice.

§211.2 DEFINITIONS

The definitions set forth in §210.3 of this chapter apply in this part.

Briefly, this section states that the company's adherence to the requirements of the entire set of regulations determined whether its output will be judged as adulterated or violative. Adherence to the requirements initially necessitates an analysis of all current operations within the company that affect the quality of the finished marketed product. Such an analysis serves as a framework for structuring decision and information flows between managers, operators, scientists, technicians, and other personnel who regulate product quality. An analysis of current conditions also divides the flow of materials into discrete, sequential operations from the receipt and sampling of raw materials to final accountability computations during the market distribution, in order that critical procedures can be specified and more closely examined.

The first step is to evaluate the chances of establishing and maintaining a good quality control program. The first list, therefore, is a description of the organization.

1. Name of company
2. Address
3. Telephone
4. Number of years in business
5. How is the company controlled?
 - ☐ Independent ☐ Subsidiary
 - a. Parent company
 - b. Address
6. Ownership
 - ☐ Corporation ☐ Partnership
 - ☐ Private ☐ Other
7. Field of operation
 - ☐ Domestic ☐ Foreign
8. Type of operation
 - ☐ Manufacturer ☐ Repacker
 - ☐ Packer ☐ Other
9. Extent of Operations
 - Plant locations* *No. of buildings* *No. of employees*
10. Current approvals
 - ☐ DA registration ☐ VA contract
 - ☐ Defense personnel ☐ Other

11. Membership in trade associations (show professional interest)
 - _____ Pharmaceutical Manufacturers Associations (i.e., PhRMA)
 - _____ The Proprietary Association
 - _____ National Pharmaceutical Council
 - _____ Parenteral Drug Association
 - _____ Drug and Allied Products Guild
 - _____ Other
12. Attendance at pharmaceutical meetings related to manufacturing and quality assurance operations.

Person Position Meetings attended/Date

Dissemination of proceedings to managers and supervisory personnel.

Lecturer Subject Personnel in Attendance Date
13. To whom does it sell (approximate percentage of sales)?
 - _____ Wholesaler _____ Hospital _____ Physician _____ VA
 - _____ Direct pharmacy _____ Defense personnel _____ Other
14. How large is the sales force?
15. What consultant services are used (including outside laboratories)?

Consultant:

Training:

Position when not consulting:

Responsibility:

Time per month:
16. In order for quality control to function properly, key executives must be appropriately educated, trained, and experienced. They should be approachable and sensitized by training or experience to quality control problems.

<i>Title</i>	<i>Name</i>	<i>Education</i>	<i>Training</i>	<i>Experience</i>
President				
Vice-President				
Sales Manager				
Medical Director				
Plant Manager				
Engineering Manager				
Production Manager				
Quality Control Director				
Laboratory Head				
17. Define the functional organization structure, including in detail all functions that contribute to acceptance or rejection decision for a product or its components.

Who has the authority to:

- a. reject defective material
- b. approve rework of salvageable material
- c. dispose of nonsalvageable material

It is important that quality control and production be kept separate and equal, usually by having the quality control manager and production manager report to the same executive, the plant manager.

It is prudent to permit personnel within both functions the authority to temporarily sequester material considered to be defective or potentially deficient while an appropriate investigation is made. The quality control function alone should have ultimate responsibility for removing a product at any stage in its processing into or from quarantine or into rejection status. Information from production and other sources should be utilized in arriving at a decision, but authority must be centralized and separated from the production function.

18. Product Information: In order to initiate quality control procedures, the dimensions of operations should be estimated. This requires the following information for the entire product line of the firm.

<i>Type and</i>	<i>Quantity</i>	<i>Quantity Packaged</i>	
<i>Product Name</i>	<i>Manufactured</i>	<i>Own label</i>	<i>Other label</i>
Tablets			
Tablets, coated			
Tablets, multilayer			
Tablets, enteric coated			
Tablets, repeat dosage			
Tablets, sustained release			
Capsules			
Capsules, sustained release			
Liquids, external			
Liquids, oral			
Liquids, oral, sustained release			
Ophthalmic solutions			
Parenteral, sterile fill			
Parenteral, sterilized			
Syringe, prefilled			
Suppositories			
Granules, oral			
Powders			
Aerosols			
Aerosols, metered dose			
Sterile dressings			

How are the products promoted? (Obtain samples and package inserts.) ____ Professional journal ____ Lay journal ____ Internet
 ____ Newspaper ____ Other

The same procedures should be followed in assessing the operations of all outside contractors who contribute to the production of the finished pharmaceutical.

Attention should be focused on the critical concepts of a quality control system. The production cycle for each drug must be controlled so that optimum quality levels can be attained for each manufacturing sequence. The efforts of all personnel making product integrity decisions during processing must be coordinated and standardized to attain these desired levels. The materials and accompanying information flow through production must demonstrate that control, engineering, and production management have determined potential sources of error and have introduced control procedures to minimize the possibility.

A model of material and information flows for operations should show complete quality control surveillance of all operations involved with drug production, adequate information exchange to monitor and control this surveillance, and records that document all activity. The flow chart in Figure 1 depicts one model for an analysis of current operations that incorporates these considerations. More

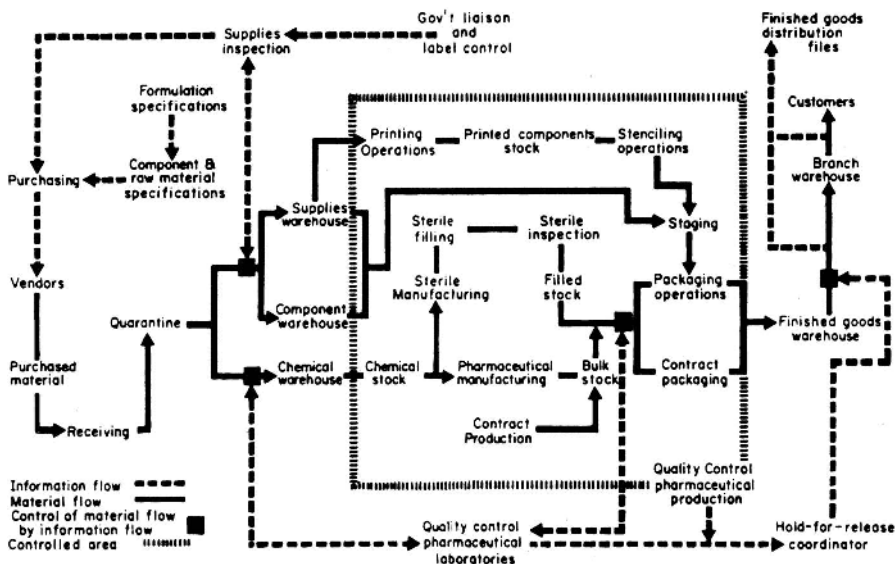


Figure 1 Information and material flow with quality control surveillance.

specific documentation and information requirements necessary to achieve control will be suggested in relevant CGMP chapters.

CGMP

Much of the foregoing pages of this chapter applies similarly to “FINISHED HOMEOPATHIC DRUGS” and to this purpose we make some special recommendations below.

The recent increase in popularity of Homeopathic Drugs presents opportunities for smaller manufacturers, exporters, and importers.

Those of us with long memories remember many popular homeopathic remedies that were sold in pharmacies in the first third of the 20th century. A favorite brand with enumerated remedies from 1 through the nineties was Humphreys Homeopathic Remedies. But homeopathy as a competitive branch of medicine had been vanquished by aliopathy, and persons licensed as homeopathic physicians were “grandfathered” into medical doctor licenses in all states.

In fact, in the great legislation that established the new drug approval procedure for the first time within the FFDC Act, President Roosevelt chose a New York Senator who was a former homeopathic physician to carry the ball in Congress, Dr. Royal S. Copeland.

Thus, although in the study of pharmacy we had all to study botany and pharmacognosy, which formed the background for homeopathic drug development, emphasis was placed on studies involving the aliopathic armamentarium and its consistency of standards based on current scientific methodology.

When as a professor at a pharmacy college or law school, I reached 201(9) of the FFDC Act, I would always invite students to visit the local homeopathic hospital and examine the Homeopathic Pharmacopeia. Of course, that in all my experience remained an assignment unmet.

The reader should recall that Section 201(g)(1) of the Act defines the term “drug” to mean articles recognized in the official *United States Pharmacopeia* (USP), the official *Homeopathic Pharmacopeia of the United States* (HPUS), or official *National Formulary* (NF) or any supplement to them; and articles intended for use in the diagnosis, cure, mitigation, treatment, or the prevention of the disease in man or other animals; articles (other than food) intended to affect the structure or any function of the body of man or other animals; and articles intended for use as a component of any articles specified in the above. Whether or not they are official homeopathic remedies, those products offered for the cure, mitigation, prevention, or treatment of disease conditions are regarded as drugs within the meaning of Section 201(g)(1) of the Act. And as drugs they are patently subject to the CGMP’s with some reservations I have noted. Homeopathic drugs generally must meet the standards for strength, quality, and purity set forth in

the Homeopathic Pharmacopeia. Section 501(b) of the Act (21 U.S.C. 351) provides in relevant part:

Whenever a drug is recognized in both the United States Pharmacopeia and the Homeopathic Pharmacopeia of the United States it shall be subject to the requirements of the United States Pharmacopeia unless it is labeled and offered for sale as a homeopathic drug, in which case it shall be subject to the provisions of the Homeopathic Pharmacopeia of the United States and not to those of the United States Pharmacopeia.

Supplemental Information Regarding Homeopathic Drugs for those readers interested in import, export, interstate commerce in such products. The FDA compliance policy guide has provided this information in main part:

CONDITIONS UNDER WHICH HOMEOPATHIC DRUGS MAY BE MARKETED (CPG 7132.15)

BACKGROUND:

The term “homeopathy” is derived from the Greek words *homeo* (similar) and *pathos* (suffering or disease). The first basic principles of homeopathy were formulated by Samuel Hahnemann in the late 1700s. The practice of homeopathy is based on the belief that disease symptoms can be cured by small doses of substances that produce similar symptoms in healthy people.

The Federal Food, Drug and Cosmetic Act (the Act) recognizes as official the drugs and standards in the *Homeopathic Pharmacopeia of the United States* and its supplements [Sections 201 (g) (1) and 501 (b), respectively]. Until recently, homeopathic drugs have been marketed on a limited scale by a few manufacturers who have been in business for many years and have predominantly served the needs of a limited number of licensed practitioners. In conjunction with this, homeopathic drug products historically have borne little or no labeling for the consumer.

Today the homeopathic drug market has grown to become a multimillion dollar industry in the United States, with a significant increase shown in the importation and domestic marketing of homeopathic drug products. Those products that are offered for treatment of serious disease conditions must be dispensed under the care of a licensed practitioner. Other products offered for use in self-limiting conditions recognizable by consumers may be marketed OTC.

This document provides guidance on the regulation of OTC and prescription homeopathic drugs and delineates those conditions under which homeopathic drugs may ordinarily be marketed in the U.S. Agency compliance personnel should particularly consider whether a homeopathic drug is being offered for use (or promoted) significantly beyond recognized or customary practice of homeopa-

thy. If so, priorities and procedures concerning the agency's policy on health fraud would apply. (See CPG 7150.10 "Health Fraud-Factors" in Considering Regulatory Action" 6/5/87.)

DEFINITIONS:

The following terms are used in this document and are defined as follows:

1. *Homeopathy*: The practice of testing the syndromes and conditions that constitute disease with remedies that have produced similar syndromes and conditions in healthy subjects.
2. *Homeopathic Drug*: Any drug labeled as being homeopathic that is listed in the *Homeopathic Pharmacopeia of the United States* (HPUS), an addendum to it, or its supplements. The potencies of homeopathic drugs are specified in terms of dilution, i.e., $1\times$ (1/10 dilution), $2\times$ (1/100 dilution), etc. Homeopathic drug products must contain diluents commonly used in homeopathic pharmaceuticals. Drug products containing homeopathic ingredients in combination with non-homeopathic active ingredients are not homeopathic drug products.
3. *Homeotherapeutics*: Involves therapy that utilizes drugs that are selected and administered in accordance with the tenets of homeopathy.
4. *Homeopathic Pharmacopeia of the United States* (HPUS): A compilation of standards for source, composition, and preparation of homeopathic drugs. HPUS contains monographs of drug ingredients used in homeopathic treatment. It is recognized as an official compendium under Section 201 (j) of the Act.
5. *Compendium of Homeotherapeutics*: An addendum to the HPUS that contains basic premises and concepts of homeopathy and homeotherapeutics; specifications and standards of preparation, content, and dosage of homeopathic drugs; a description of the proving* process used to determine the eligibility of drugs for inclusion in HPUS; the technique of prescribing the therapeutic application of homeopathic drugs; and a partial list of drugs that meet the criteria of the proving process and are eligible for inclusion in HPUS and other homeopathic texts.
6. *Extemporaneously Compounded OTC Products*: Those homeopathic drug products that are often prepared by dilution to many variations of potency from stock preparations, and that: (1) have at least one OTC indication; (2) are prepared pursuant to consumers' oral or written re-

* A proving is synonymous with the homeopathic procedure (identified in HPUS as a "Research Procedure") which is employed in healthy individuals to determine the dose of a drug sufficient to produce symptoms.

quests; and (3) are not generally sold from retail shelves. Those products that are prescription drugs only cannot be provided to consumers as extemporaneously compounded OTC products but may only be prepared pursuant to a prescription order.

7. *Health Fraud*: The deceptive promotion, advertisement, distribution or sale of articles, intended for human or animal use, that are represented as being effective to diagnose, prevent, cure, treat or mitigate disease (or other conditions), or provide a beneficial effect on health, but that have not been scientifically proven safe and effective for such purposes. Such practices may be deliberate, or done without adequate knowledge or understanding of the article.

CGMP Requirements

All firms that manufacture, prepare, propagate, compound, or otherwise process homeopathic drugs must register as drug establishments in conformance with Section 510 of the Act and 21 CFR 207. Further, homeopathic drug products must be listed in conformance with the sections above. (*Note*: For a given product, variations in package size and potency are not required to be listed on separate forms 2657 but instead may be listed on the same form.) Homeopathic drug products must be packaged in accordance with Section 502(g) of the Act. Homeopathic drug products must be manufactured in conformance with current good manufacturing practice, Section 501(a)(2)(B) of the Act and 21 CFR 211. However, due to the unique nature of these drug products, some requirements of 21 CFR 211 are not applicable, as follows:

1. Section 211.137 (Expiration dating) specifically exempts homeopathic drug products from expiration dating requirements.
2. Section 211.165 (Testing and release for distribution): In the Federal Register of April 1, 1983 (48 FR 14003), the Agency proposed to amend 21 CFR 211.165 to exempt homeopathic drug products from the requirement for laboratory determination of identity and strength of each active ingredient prior to release for distribution.

Pending a final rule on this exemption, this testing requirement will not be enforced for homeopathic drug products.

REGULATORY ACTION GUIDANCE:

Those firms marketing homeopathic drugs that are not in compliance with the conditions described above will be considered for regulatory follow-up. The Office of Compliance, HFD-304, Center for Drug Evaluation and Research, should be consulted before warning letters are issued.

Recommendations for the issuance of warning letters or other regulatory sanctions must be submitted in conformity with the Regulatory Procedures Manual and other Agency guidance concerning the review of regulatory actions.

A product's compliance with requirements of the HPUS, USP, or NF does not establish that it has been shown by appropriate means to be safe, effective, and not misbranded for its intended use. A guide to the use of homeopathic drugs (including potencies, dosing, and other parameters) may be found by referring to the following texts: *A Dictionary of Practical Materia Medica* by John Henry Clarke, M.D. (3 volumes; Health Science Press) and *A Clinical Repertory to the Dictionary of Materia Medica* by John Henry Clarke, M.D.

For readers interested in labeling for homeopathic drugs, see Chapter 8 below.

The American Medical Association's House of Delegates has expressed the view that dietary supplements should be required to meet USP compendial standards prior to marketing. This would put them in category not too unlike that of homeopathic drugs. That should not be, since homeopathic drugs, as discussed elsewhere, do make claims in areas of prevention, treatment, or mitigation of disease.

Obviously there is some confusion here in the minds of physicians reflecting their consumer patients' attitudes toward dietary aids.

**SUPPLEMENTARY INFORMATION AS TO CGMPs FOR
MEDICAL DEVICES AS PROVIDED BY FOOD AND DRUG
ADMINISTRATION (HFZ)341) 2098 GAITHER RD.
ROCKVILLE, MD 20850 (301-594-4648)**

Manufacturers establish and follow quality systems to help ensure that their products consistently meet applicable requirements and specifications. The quality systems for FDA regulated products (food, drugs, biologics, and devices) are known as CGMPs. CGMP requirements for devices (part 820 (21 CFR part 820)) were first authorized by section 520(f) of the Federal Food, Drug and Cosmetic Act (the Act) (21 U.S.C. 360j(f)), which was among the authorities added to the Act by the Medical Device Amendments of 1976 (Pub. L. 94-295). The Safe Medical Devices Act (the SMDA) of 1990 (Pub. L. 101-629), enacted on November 28, 1990, amended section 520(f) of the Act, providing FDA with the explicit authority to add preproduction design validation controls to the CGMP regulation. The SMDA also added a new section 803 to the Act (21 U.S.C. 383) which, among other things, encourages FDA to work with foreign countries toward mutual recognition of CGMP requirements.

FDA undertook the revision of the CGMP regulation in part to add the design controls authorized by the SMDA to the CGMP regulation, and in part

because the agency believes that it would be beneficial to the public, as well as the medical device industry, for the CGMP regulation to be consistent, to the extent possible, with the requirements for quality systems contained in applicable international standards, namely, the International Organization for Standards (ISO) 9001:1994 “Quality Systems—Model for Quality Assurance in Design, Development, Production, Installation, and Servicing” (Ref. 1), and the ISO working draft revision of ISO/DIS 13485 “Quality Systems—Medical Devices—Supplementary Requirements to ISO 9001,” among others. The preamble to the November 23, 1993, proposal contained a detailed discussion of the history of the device CGMP regulation, from the agency’s initial issuance of the regulation through FDA’s decision to propose revising the regulation.

The agency’s working draft embraces the same “umbrella” approach to CGMP regulation that is the underpinning of the existing CGMP regulation. Thus, because this regulation must apply to so many different types of devices, the regulation does not prescribe in detail how a manufacturer must produce a specific device. Rather, the regulation lays the framework that all manufacturers must follow, requiring that the manufacturer develop and follow procedures, and fill in the details, that are appropriate to a given device according to the current state-of-the-art manufacturing for that specific device. FDA has made further changes to the proposed regulation, as the working draft evidences, to provide manufacturers with even greater flexibility in achieving the quality requirements.

FDA met with the Global Harmonization Task Force (GHTF) Study Group in early March 1994, in Brussels, to compare the provisions of the proposal with the provisions of ISO 9001:1994 and European National (EN) standard EN 46001 “Quality Systems—Medical Devices—Particular Requirements for the Application of EN 29001.” The GHTF includes: Representatives of the Canadian Ministry of Health and Welfare; the Japanese Ministry of Health and Welfare; FDA; and industry members from the European Union, Australia, Canada, Japan, and the United States. The participants at the GHTF meeting favorably regarded FDA’s effort toward harmonization with international standards. The GHTF submitted comments, however, noting where FDA could more closely harmonize to achieve consistency with quality system requirements worldwide. Since the proposal was published, FDA has also attended numerous industry and professional association seminars and workshops, including ISO Technical Committee 210 “Quality Management and Corresponding General Aspects for Medical Devices” meetings, where the proposed revisions were discussed. See also ISO 9000 and Medical Device Regulation in the European Union-James W. Kolka, Vol 11, no. 3 (Oct 1990), in the F.D.C.M.D. Law Digest.

The original period for comment on the proposal closed on February 22, 1994, and was extended until April 4, 1994. Because of the heavy volume of comments and the desire to increase public participation in the development of the quality system regulation, FDA decided to publish this notice of availability

in the *Federal Register* to allow comment on the working draft, to be followed by two public meetings, as described below, before issuing a final regulation.

Having addressed the many comments received, the agency has framed a final rule that achieves the public health goals to be gained from implementation of quality systems in the most efficient manner.

Following study of this chapter, it might be helpful for staff review to discuss specific guides provided by the FDA to their field staff and others, that are pertinent as Regulatory Action Guidance.

Sec. 480.100 Requirements for Expiration Dating and Stability Testing (CPG 7132a.04)

Revisions to 21 CFR Part 211, Current Good Manufacturing Practices for Finished Pharmaceuticals (CGMP) introduced requirements concerning expiration dating (21 CFR 211.137) and stability testing (21 CFR 211.166) which became effective September 29, 1979. The purpose of this guide is to delineate those situations in which the Center is prepared to consider regulatory action.

POLICY:

If any of the following situations exist, recommend appropriate action (e.g., * warning letter or seizure) to HFD-300: *

1. Lack of assurance that a product labeled as sterile has been tested to ascertain that the container and closure can maintain a sterile state throughout the labeled shelf life.
2. Lack of a written stability program for bulk drug substances or an indication that it is either inadequate or not being followed.
3. Lack of an expiration date on finished dosage forms or a written stability program. See CPG 7132a.10 (See Sec. 480.300).
4. Lack of a labeled date indicating stability after reconstitution or lack of studies to support the appropriateness of that date.
5. Lack of an ongoing testing program to verify product stability after the shelf life has been determined appropriate.
6. Lack of assurance that meaningful, specific, or reliable test methods and storage conditions are employed.
7. Lack of assurance that the currently marketed container or closure will provide adequate protection of the drug product.
8. Lack of follow-up studies at the labeled storage conditions or, if there are no storage conditions specified, at room temperature, for drug products for which the shelf life was determined by accelerated studies.
9. Lack of assurance of the effectiveness of any preservatives used throughout the labeled shelf life.
- * 10. Lack of an adequate number of batches (i.e., less than three) employed as

the basis for either confirming a tentative expiration date or establishing the long-term stability of the product.

11. Distribution of product past the labeled expiration date.*

* Material between asterisks is new or revised. *

Issued: 6/20/85

Reissued: 9/4/87, 3/95

Sec. 480.300 Lack of Expiration Date of Stability Data (CPG 7132a.10)

BACKGROUND:

* The CGMP regulations (21 CFR 211.137) have required that drug products packaged since September 29, 1979, bear an expiration date which is supported by appropriate stability data, with limited exceptions. OTC drug products which have no dosage limitation and which are stable for at least three years as demonstrated by appropriate data are exempt from the requirement to bear an expiration date. Homeopathic drugs, while required to have a limited evaluation of stability, are also exempt from the requirement to bear an expiration date. Additionally, allergenic extracts that are labeled "No U.S. Standard of Potency" are exempt from the requirements to be labeled with an expiration date and the performance of stability studies. *

Section 211.166 requires a firm to have a written stability program, the results of which are to be used in determining appropriate storage conditions and a product's expiration date and specifies what must be included in the stability program.

In addition, the USP requires that the labels of all pharmacopeial dosage forms bear an expiration date.

REGULATORY ACTION GUIDANCE:

District offices are authorized to issue * Warning Letters without Office of Compliance, HFD-300 *, review under the following circumstances:

1. A non-compendial drug product intended for internal use does not bear an expiration date and is not exempt by regulations.

Charge: 501(a)(2)(B), 21 CFR 211.137.

2. A prescription drug product for which it has been determined that stability studies do not exist.

Charge: 501(a)(2)(B), 21 CFR 211.166

Examples of the wording to be used in a * warning letter * are as follows:

501(a)(2)(B) Your product, (name of product), is adulterated in that the controls used

for the manufacture, processing, packing, or holding of this drug product are not in conformance with current good manufacturing practice regulations (Title 21, Code of Federal Regulations, Parts 210 and 211).

Specific Violations are:

There is no assurance that the product meets applicable standards of identity, strength, quality, and purity at the time of use in that it does not bear an expiration date (211.137).

You have not performed stability testing of your product and therefore are unable to appropriately determine storage conditions designed to assure the stability of your drug product (211.166).

NOTE: If appropriate, misbranding [502(g)] may be charged when a USP drug product intended for internal use does not bear an expiration date and is not exempt by regulations. Example of the wording to be used in a * warning letter: *

502(g) The article (name of the drug product) is misbranded in that it purports to be a drug, the name of which is recognized in an official compendium and the label fails to bear an expiration date as prescribed therein.

All other cases should be referred to the Office of Compliance, * HFD-300 *, or as identified in * CPG 7132a.04 (See Sec. 480.100) or * specific compliance programs, in the usual manner.

* Material between asterisks is new or revised *

Issued: 1/16/84

Revised: 9/4/87, 3/95

3

Organization and Personnel (Subpart B)

§211.22 RESPONSIBILITIES OF QUALITY CONTROL UNIT

(a) There shall be a quality control unit that shall have the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging materials, labeling, and drug products, and the authority to review production records to assure that no errors have occurred, or, if errors have occurred, that they have been fully investigated. The quality control unit shall be responsible for approving or rejecting drug products manufactured, processed, packed, or held under contract by another company.

(b) Adequate laboratory facilities for the testing and approval (or rejection) of components, drug product containers, closures, packaging materials, in-process materials, and drug products shall be available to the quality control unit.

(c) The quality control unit shall have the responsibility for approving or rejecting all procedures or specifications impacting on the identity, strength, quality, and purity of the drug product.

(d) The responsibilities and procedures applicable to the quality control unit shall be in writing; such written procedures shall be followed.

The regulations clearly assign to the quality control (QC) unit responsibility for approval or rejection of components, in-process materials, and products. At one time the attainment of quality standards relied heavily on testing and inspec-

tion by QC—quality was inspected into components and products. Since QC testing is usually after the event, and also relies on the evaluation of a relatively small sample, this approach was seen by some as both ineffective and inefficient. It also tended to separate accountability for production and quality.

The CGMPs focus all responsibility for quality onto the QC unit. There are no defined responsibilities for production management—unlike the European and World Health Organization (WHO) guidelines ([see Chapter 21](#)), which define both separate and joint responsibilities for these functions. This latter approach more clearly emphasizes that the consistent achievement of quality standards requires a team effort.

A more effective approach has been to design quality into products during the development phase and then to build in additional assurance during production. The regulations support this approach. New products are usually developed by a research and development unit, which will draft appropriate specifications. These must then be reviewed and approved by QC, which serves as an independent double-check on this important parameter.

Within the production operations all quality-impacting procedures and systems are to be approved by QC. Typically, these include such procedures as standard operating procedures (SOPs), process validation protocols, supplier certification protocols, complaint handling, process control procedures, and even design of buildings. Since some of these systems are “owned” by other functions, it is essential that QC have effective procedures to ensure that such systems are reviewed in a timely manner and that changes cannot be introduced without approval. During 1985 and 1986 several companies had serious problems associated with changes in formulations and manufacturing processes, which then failed to comply with requirements of NDA and ANDA documentation. These discrepancies resulted in halting of distribution and recalls, with significant loss of revenue to the companies involved. Some of these situations occurred because economies and expedition overwhelmed inadequate approval systems.

QC is also responsible for approving or rejecting labeling. This responsibility lies in two areas. First, new or modified labeling should be reviewed to ensure that it complies with the ANDA, NDA, OTC monograph, or other official requirements that are applicable. This checking may be delegated to other functions, but QC must assure that the checkers are qualified to perform their function and that they have done so. Second, incoming labeling supplies are to be evaluated to assure they are correct. These responsibilities do not apply to promotional literature.

The approval/rejection responsibility also applies to operations contracted out to other companies. This does not necessarily require any additional or duplicate testing. Provided the contractor has adequate procedures and is in full compliance with CGMPs, it should only be necessary to compare the test data with specification and with data from previous batches to identify trends.

Confirmation of the adequacy of the contractor will normally involve an audit and testing in parallel for a period of time; periodic reevaluation should occur.

The regulations require adequate laboratory facilities to be available to the QC unit. This clearly allows use of outside laboratories where necessary, but these should be comprehensively evaluated before use.

The FDA emphasis for QC is on release and/or rejection authority. While this is important, the regulations ignore the ever-increasing importance of other activities by QC that provide positive impact on quality. These include creation of quality awareness, involvement in product design and development, design and provision of quality training, facilitation for quality improvement, analysis of quality trend data to identify improvement needs and opportunities, identification of quality metrics, and collection and dissemination of quality benchmarking data. These additional activities all enhance the awareness and involvement of senior management, thereby assuring greater emphasis and attention to quality by all functions.

No guidance is provided about the actual organization of the QC department, and a wide range of viable alternatives are in effect. One of the simplest, but very effective, is the subdivision into quality control—all inspection and testing and quality assurance—all systems and procedures including batch review and audit. With the increased reliance on non-QC personnel for quality-related activities, such as in-process control and customer complaint coordination, the role of the quality assurance (QA) unit has become critical. The regulations essentially expect the QC/QA function to provide an independent policy-type role, to monitor the entire production process from purchasing of materials to distribution and use of the product. The function should also be proactive by evaluating data on processes, materials, and suppliers and recommending changes that will improve efficiency and consistency. QC should be a resource that plays a positive role in improving profitability. More will be said about this in future chapters.

The responsibilities of the QC unit with respect to acceptance/rejection has led to extensive discussion on organizational reporting lines. Obviously, the QC function cannot report to the person who is held directly accountable for production. This could result in undue pressure being brought to bear to release marginal materials or products. In an enlightened company where everyone is fully aware of the importance of quality and committed to its achievement, this should not be an issue. However, some companies have gone a step further by insisting that the QC unit should report outside of the plant operations to a group QC function or other scientific or technical function. This arrangement certainly provides an added level of independence and appears to be favored by the FDA. However, as previously expressed, quality standards cannot be assured by a police approach. With a totally independent QC unit, there is likely to be a chance of divided responsibility—production to produce and QC to confirm quality. It is

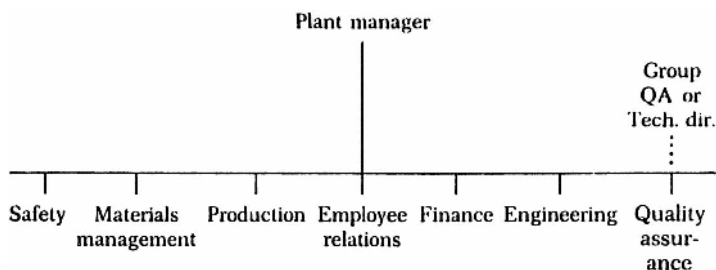


Figure 1 Typical plant organization.

preferable that the entire plant operate as a quality-aware team, every individual being expected to perform his or her job in such a manner as to achieve the quality standards. QC then becomes a supporting resource. This is more likely to occur if the QC unit reports directly to the leader of the plant team—the plant manager. An adequate degree of independence can be incorporated into the organization by having a clearly defined functional reporting (“dotted line”) relationship to a suitable scientific professional in the organization (Figure 1). This approach encourages a team spirit, which will result in a higher and more consistent achievement of quality standards. Even the review of potential accept/reject decisions should be handled by the management team so that everyone is involved in understanding the cause of the problem, the implications of the ultimate decision, and the need for appropriate corrective action. In the event that the team is in favor of acceptance when QC consider rejection to be correct, the final decision resides with QC; the plant manager cannot override.

Some companies have taken the team approach a stage further by the introduction of self-managed work teams. The various functions or disciplines are incorporated into the team, which can be responsible for all its operational requirements. This can include, in extreme cases, hiring of new team members, discipline, allocation of wage increases or bonuses, work scheduling, product testing, and release/rejection decisions. In these instances there still needs to be an independent QC evaluation for final release/rejection to satisfy the regulations.

§211.25 PERSONNEL QUALIFICATIONS

(a) Each person engaged in the manufacture, processing, packing, or holding of a drug product shall have education, training, and experience, or any combination thereof, to enable that person to perform the assigned functions. Training shall be in the particular operations that the employee performs and in current good manufacturing practice (including the current good manufac-

turing practice regulations in this chapter and written procedures required by these regulations) as they relate to the employee's functions. Training in current good manufacturing practice shall be conducted by qualified individuals on a continuing basis and with sufficient frequency to assure that employees remain familiar with CGMP requirements applicable to them.

(b) Each person responsible for supervising the manufacture, processing, packing, or holding of a drug product shall have the education, training, and experience, or any combination thereof to perform assigned functions in such a manner as to provide assurance that the drug product has the safety, identity, strength, quality, and purity that it purports or is represented to possess.

(c) There shall be an adequate number of qualified personnel to perform and supervise the manufacture, processing, packing, or holding of each drug product.

The development and training of employees, at all levels, should be seen as a continuous process (Figure 2) in which performance appraisal plays a key role.

The GMP regulations do not attempt to define the education, knowledge, skills, or experience required for the different types of job within a pharmaceutical company. This is significantly different from the European and WHO guidelines, which do specify the knowledge and experience requirements for those individuals designated as responsible for production and quality. The consistent achievement of quality standards requires understanding of, and compliance with, established procedures. Consequently, initial screening should select only those individuals who have such basic skills as reading, writing, and numeracy. An employee who cannot understand written instructions will find it difficult to fol-

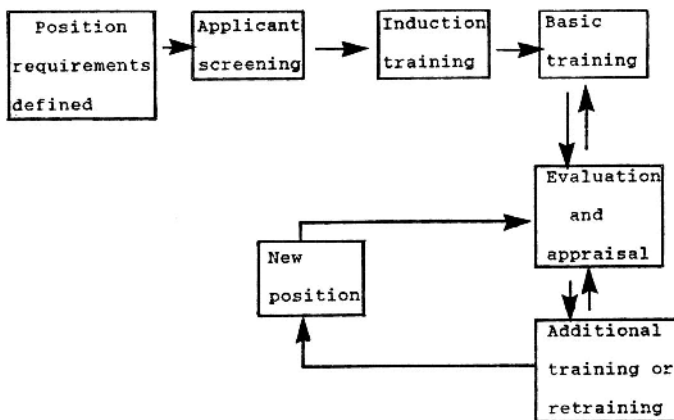


Figure 2 Training and development cycle.

low procedures, an inability to write coherently will inhibit the recording of atypical situations, while a lack of numeracy could make it impossible to perform certain in-process testing such as statistical process controls. For certain positions color vision may also be important, and some 10% of the population have some degree of color vision problem.

In addition to these basic skills required by every employee, there are specific requirements for certain jobs, such as higher qualifications in engineering, chemistry, microbiology, etc. In order to define these additional requirements it is important to perform a knowledge and skills assessment for each job category. Because of the changing environment in which we work it is essential to reevaluate these needs from time to time.

Preemployment screening for the purpose of identifying potential security risks is of special importance when the pharmaceutical manufacture involves the handling of controlled substances. This screening must not only include careful scrutiny of the potential employee's personal and previous employment references, but also whatever review of criminal background as may be possible. The Drug Enforcement Agency (DEA) position on employee screening is set out in 21 CFR 1301.90. Subsequent parts, 1301.91, 1301.92, and 1301.93, indicate the tenor of the employer's responsibility as it must be conveyed to the employee and describe the sources of information to be used in employee checks.

While the dangers of insecurity with respect to controlled substances are of concern to the DEA as they may involve criminal acts and frustrate accountability, the effect of loss or diversion of any ingredient or product will reflect as a CGMP failure.

Once accepted for employment, the initial, or induction, training takes place. This usually occurs on the first day and includes background on the industry, the company—its policies and procedures—and some fundamentals on the importance of the employee's role to the health and well-being of the ultimate consumer. This session tends to be somewhat general in nature and should be followed by the more specific basic training.

Basic training will usually take place over a period of time during which the new employee will be closely supervised. During this stage the employee must be fully trained in all relevant techniques associated with the equipment involved and fully understand the procedures to be followed, and must be aware of the potential problems that can be created by nonadherence to these procedures. Such problems could include production of substandard material resulting in rework or rejection if identified in-house or in potential consumer harm, litigation, and recall if not detected until in the marketplace. All these consequences add cost and some also have the potential to erode consumer confidence.

Training programs must include appropriate evaluation steps. These will usually involve some type of evaluation at the end of each module followed by

on-the-job appraisal to confirm that the lessons learned have been put into practice. Repeat training should be initiated when necessary. The regular employee performance appraisal process should also identify further training needs—as refreshers to existing knowledge and skills, to meet the changing needs of the operation, or in preparation for a job change requiring additional skills.

Education and training records must be maintained and kept current; FDA inspectors may ask for confirmation of adequate training.

The responsibility for training of employees should reside with departmental management. However, the QC department should monitor or audit to ensure that the appropriate training has been given. This could include review of training module content and also of training records. Additionally, QC staff themselves are likely to be involved in providing some of the training.

Training, although essential, is more effective in a supportive environment. If management, by example, demonstrate that compliance with procedures is important and encourage participation in improvements, then training will be put into practice. The acknowledgment of achievement by public recognition or remuneration, often termed positive reinforcement, has a significant impact. The demonstration by example is further illustrated in a later section.

§211.28 PERSONNEL RESPONSIBILITIES

- (a) Personnel engaged in the manufacture, processing, packing, or holding of a drug product shall wear clean clothing appropriate for the duties they perform. Protective apparel, such as head, face, hand, and arm coverings, shall be worn as necessary to protect drug products from contamination.
- (b) Personnel shall practice good sanitation and health habits.
- (c) Only personnel authorized by supervisory personnel shall enter those areas of the buildings and facilities designated as limited-access areas.
- (d) Any person shown at any time (either by medical examination or by supervisory observation) to have an apparent illness or open lesions that may adversely affect the safety or quality of drug products shall be excluded from direct contact with components, drug product containers, closures, in-process materials, and drug products until the condition is corrected or determined by competent medical personnel not to jeopardize the safety or quality of drug products. All personnel shall be instructed to report to supervisory personnel any health conditions that may have an adverse effect on drug products.

This element of the regulations is extremely limited. The only stated responsibilities of personnel relate to personal hygiene. There are no assigned re-

sponsibilities to comply with defined procedures or to advise management of deviations or problems.

The wearing of uniforms for manufacturing and control operations is not mandated, only that clothing shall be clean and appropriate for the duties being performed. In defining what clothing is appropriate it is necessary to consider the end purpose. For example, it would be inappropriate to require hair covering to protect the product from the inadvertent ingress of hair and then to allow employees to wear clothing that incompletely covered the hair, did not cover beards or moustaches, or left the arms uncovered. Yet such situations do exist.

The use of plant uniforms is generally a more satisfactory way of maintaining adequate standards of dress and the following guidelines may be applied:

1. A sufficient amount of clean uniforms is provided so that changes can be made at an adequate defined frequency or whenever they became soiled.
2. Washing and sanitation procedures should be checked to confirm their effectiveness.
3. Employees in special clean areas should wear only lint-free garments to prevent shedding.
4. Garments should be designed and use material that maximizes personal comfort.
5. The range of clothing available would normally include:
 - a. Hats or hair cover
 - b. Beard and moustache covers
 - c. Coveralls—preferably with no pockets, or pockets suitably designed to prevent articles falling out
 - d. Disposable gloves
 - e. Foot covers or shoes
 - f. Masks
 - g. Safety glasses or goggles
 - h. Appropriate clean-room suits for sterile areas
6. Employees should be shown how and when to wear the appropriate clothing.
7. Work clothing should not be worn outside of the appropriate plant area, and changing rooms should be available.

The continued wearing of such clothing in cafeteria areas during breaks should also be evaluated. Food particles in and on clothing can introduce bacterial, fungal, and yeast contamination. Obviously, operators in sterile areas will change prior to leaving the area, and this may be desirable for some other areas, especially to minimize the potential for cross-contamination.

Compliance with the requirements that production processes should not

be exposed to employees who are sick starts with the preemployment medical examination. This will normally include some medical history, chest x-ray, Wassermann test, and tuberculosis test. Employees should require a fitness statement from a physician, either company or personal, for return to work after sick leave greater than a specified period (one week). Annual medical reexaminations are sometimes required. Because some locations have stringent concerns as to invasions of employee privacy, personnel should be guided by legal advice that is current. There should be a liberal policy for those who feel fit for work but show symptoms of the common cold or other nondisabling illness. Employees will be reluctant to report these conditions if they are punished by being sent home, having their pay reduced, or being told to continue work since “it doesn’t really matter.” Ideally, these employees should be allowed to work at tasks in which they cannot contaminate products and at their usual rate of pay.

Separating an ill worker or one with open lesions from the product by use of gloves, masks, or special clothing is not recommended. The discomfort involved in their use tempts the worker to discard them when not being observed. The requirement of this section to report adverse health conditions will not be effective unless a set of specific conditions to be reported is provided. Again, be guided by current legal advice as to the substance and receipt of such information.

The primary objective of this section of the regulations is to protect the product from potential contamination from personnel—particulate matter including hair, fibers, and outside “dirt,” cross-contamination carried on clothing from other processes, microorganisms shed from skin and from the mouth and nose. However, an employer also has a responsibility to protect the employee from unacceptable exposure to the materials being handled, many of which have physiological properties. Where potential exposure is to very potent materials, testing of blood or urine samples may be warranted. Wherever possible, barrier or containment facilities or equipment should be used to protect personnel from extremely hazardous materials. The use of masks or breathing equipment should only be used as the sole precaution in rare circumstances or for less hazardous materials.

§211.34 CONSULTANTS

Consultants advising on the manufacture, processing, packing, or holding of drug products shall have sufficient education, training, and experience, or any combination thereof, to advise on the subject for which they are retained. Records shall be maintained stating the name, address, and qualifications of any consultants and the type of service they provide.

It is difficult to appreciate the need for this section. It is highly unlikely that a company would spend money to employ a consultant who was inadequate in education, training, or experience. Additionally, company management are accountable for any effects resulting from implementation of advice from consultant. However, this section provides a means to educate the agency as to the identity of the consultants where the FDA inspection reveals significant deficiencies.

Note that under Section 211.122(c) the QC unit must approve the qualifications of a consultant whose work may impact on the identity, strength, quality, or purity of a drug product. A more appropriate and useful topic would have been the use of contractors for either laboratory or production operations.

We therefore transmit some advice on that point.

The use of contractors for either laboratory or production operations has grown to a fairly common practice in pharmaceuticals and device manufacture. The labeler and distributor of the final finished product, in the absence of contrary agreements between the parties, bears primary commercial, civil, and regulatory responsibility in keeping with established legal theory and business custom in the United States and Europe.

Because the regulatory agency sees so much activity along the lines, they have made available compliance policy guidelines. Following, therefore, we have included CPG150.16, which typifies their view and attaches to “Status and Responsibilities of Contract Sterilizers Engaged in Sterilization of Drugs and Devices.” This touches upon Registration and all that connotes as well as the CGMPs. The reader should consider it also with respect to Chapter 11 below.

Following study of this chapter, it might be helpful for staff review, to discuss specific guides provided by the FDA to their field staff and others, that are pertinent as Regulatory Action Guidance.

COMPLIANCE POLICY GUIDELINES

Sec. 100.550 Status and Responsibilities of Contract Sterilizers Engaged in the Sterilization of Drugs and Devices (CPG 7150.16)

BACKGROUND:

Questions have been raised as to the responsibilities of a contract sterilizer under the Food, Drug and Cosmetic Act. The questions concern registration requirements under Section 510, Agency inspectional policy, documentation and validation requirements, and responsibilities of the parties to the contractual agreements.

DEFINITION:

For the purposes of this guide the following definition will apply:

Contract Sterilizer. An establishment that provides a contractual service intended to sterilize an FDA regulated product.

POLICY:

1. Responsibility of Contract Sterilizers:
Contract sterilizers are responsible for conformance with the portions of the current Good Manufacturing Practice (CGMP) regulations that pertain to the services they provide.
2. Registration:
Each contract sterilizer of a drug or device product must register as set forth under section 510 of the Act.
3. Documentation:
The finished drug or device manufacturer should maintain, as part of the master production and control record, or reference, written process specifications and documentation of the validation of the sterilization process conducted by the contract sterilizer. The finished drug or device manufacturer should also maintain, or have readily available, copies of the contract sterilizer's batch production records.
The contract sterilizer must maintain documentation of validation and the written process and production specifications and procedures necessary to assure the process is adequately completed. Contract sterilizers are also responsible for completing and maintaining batch records of all operations performed.
4. Inspections:
Contract sterilizers, as drug or device processors, are subject to the biennial inspection requirements of the Act.
5. Contractual Agreements:
The contractual agreement should specify which establishment will execute various functions. In general, the establishment which executes a given function will be primarily responsible for the CGMP's which apply to that function.
6. Sterilization Process Validation:
Sterilization processes are required by the CGMP's to be validated. The validation may be conducted by either the finished drug or device manufacturer or the contractor. The finished drug or device manufacturer has ultimate responsibility for assuring that the finished drug or device meets sterility specifications and is processed under adequate CGMP controls. The contractor who offers a sterilization process has responsibility to assure the process is effective and that adequate GMP controls are established and implemented. Therefore both parties are responsible for validation and liable to the extent that they have contributed to the noncompliance. The absence of an agreement does not remove this responsibility for either party.

NOTE: For licensed biologicals, the “Center for Biologics Evaluation and Research” holds the final manufacturer responsible for all production processes, including validations of sterilization performed under contract, whether or not the contract so states.

REGULATORY ACTION GUIDANCE:

In adverse findings are encountered during an inspection, the appropriate Center should be notified. In addition, the districts that have firms using the services of contractors outside the district should be advised of any adverse finding.

In considering regulatory, voluntary, or administrative action, the agency will regard the manufacturer as primarily responsible for assuring the compliance of the medical product. However, the contract sterilizer and the manufacturer will be held jointly responsible for those processes performed by the contractor to the extent that each party contributed to the violations. Performance of each party will be considered in determining whether one or both parties are subject to regulatory action for failure to comply with GMPs. Should regulatory action be generated as a result of inspection of the contract sterilizer, both parties should receive copies of all correspondence.

* Material between asterisks is new or revised *

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Revised: 8/31/89, 3/95

EXAMPLES OF OBSERVATIONS FROM FDA 483 CITATIONS

1. There was insufficient personnel for performance of the quality control activities in that there are no approved written procedures to include cleaning of manufacturing and laboratory equipment, maintenance and calibration of laboratory equipment, label procedures for quarantine materials, stability program, GMP training of all personnel.

2. The GMP training program is inadequate in that it does not define the type, level, and schedule of GMP training required for various employee positions; production employee training consists of a review of SOPs and on-the-job training.

SUGGESTED READINGS

1. J. Litterer, *Organizations: Structure and Behavior*, Wiley, New York, 1968.
2. E. Murray, *Motivation and Emotion*, Prentice-Hall, Englewood Cliffs, NJ, 1965.
3. E. Schein, *Organizational Psychology*, Prentice-Hall, Englewood Cliffs, NJ, 1965.

4. F. Delmore, Industry Associations and Self-Regulation, *Food, Drug, Cos. Law J.*, 24(11):557–564, 1969.
5. J. Saengen, The Key To Quality Programs, *Bull. Parent. Drug Association*, 23:197–285, 1969. This is an excellent description of one company’s quality assurance program.
6. S. H. Willig, Drug Abuse in Industry and Business 1971, Symposium Enterprises.
7. B. J. Donato, Kenneth A. Olsen, Vol 11, No. 2 (July 1994) Food Drug Cosmetic “Legal Liability For Regulatory Affairs Professionals . . .” and Medical Device Law Digest.
8. R. H. Clark and K. L. Dimond, “Compliance Plan: A Drug Company’s first line of defense . . . Vol 13, No. 2, May 1996, Food, Drug, Cosmetic and Medical Device Law Digest.
9. See also Drug Free Work Place Requirements, Fed. Register, Tues Jan 31, 1989.
10. Employee Benefits Bulletin. A Review and Analysis of Recent Developments, Sept. 1999. Alan M. Koral. Free Copies Available. 805 Third Ave. N.Y., NY. 10022.

4

Buildings and Facilities (Subpart C)

§211.42 DESIGN AND CONSTRUCTION FEATURES

(a) Any building or buildings used in the manufacture, processing, packing or holding of drug product shall be of suitable size, construction and location to facilitate cleaning, maintenance, and proper operations.

Regarding buildings and facilities, there are two major areas of concern: the external environment and the internal environment. The external environment must be amenable to the location of well-designed and constructed buildings. It is insufficient that the buildings in which the production operations are to occur are clean and orderly and of suitable size and construction. If the land, air, or water resources that surround the plant offer the potential for water damage, infestation, or contamination of any type, the facilities are in jeopardy of being judged unsuitable.

Several professional resources and functions will be involved in site selection. These are likely to include legal, real estate, and state and local government agencies, utility companies, engineers, and architects. These functions not only provide professional expertise but are able to identify possible sources of financial incentives for building in specific geographical locations.

Pertinent consideration prior to purchase, construction, or alteration of existing facilities includes the following:

1. Adequate space for future expansion.
2. Zoning laws to allow anticipated development while restricting undesirable developments in the vicinity.
3. Availability of water (quality and quantity), power, fuel, sewage and waste-stream removal.
4. Accessibility for employees (availability of public transportation), materials, and visitors (customers, suppliers).
5. Environmental issues such as site history; soil, water, and air quality; and geological and topological issues (potential for flooding, earthquakes, foundation instability).
6. Proximity of undesirable activities likely to pollute or act as a source of vermin, insects, odor, or microorganisms—such as other industries, disposal sites, or open mining.
7. Availability of a suitable labor force (people, skills, wage expectations, labor relations and attitudes, access to further education sources).
8. Ability to provide adequate security arrangements.
9. Proximity or accessibility to interrelated operations of the company—R&D, marketing, internally produced intermediates or components.
10. Political situation—government stability, trade policies and taxation (for foreign-based operations), financial incentives.

Having identified a suitable location for the facility, the site development plan is prepared and will include:

1. Compliance with appropriate laws and regulations and any additional company standards.
2. Site resources and infrastructure such as amenities, green spaces, parking (employees, delivery and distribution vehicles, visitors), road and rail access, recreation areas, site utilities, tank farms and other external storage, and protection of wetlands and other restricted environments.
3. Stormwater and waste management.
4. Site security and access—fences, guard posts, cameras.
5. Buildings—siting, layout, usage, function interrelationships for efficiency, possible expansion, surface finishes.
6. Utilities—design, layout, backup (especially for critical utilities as electricity and nitrogen for some chemical operations).
7. Equipment—design, layout, spares, capacity.
8. Traffic flow—pedestrian and vehicular (internal and external).
9. Safety—for personnel and equipment, containment for hazardous materials, sprinkler system, emergency egress, and emergency services access.

10. External architecture to take into account local environmental conditions (wind, snow, humidity) and aesthetic appearance blending local atmosphere, comparative image, and functionality.
11. Ease of maintenance—accessibility to services (service ducts), ease of cleaning, access for equipment.
12. Selection and use of experienced contractors.
13. Identification of project management responsibility.
14. Validation plans and an effective change control procedure. Provision of design and “as-built” drawings.
15. Construction materials.

- a. Walls. The position of walls should provide an orderly movement of materials and personnel and should also take into account noise levels to provide acceptable working conditions. The interrelationship of different operations should minimize the potential for cross-contamination and for component mix-up during storage and interdepartmental shipping.

Walls in manufacturing areas, corridors, and packaging areas should be of plaster finish on high-quality concrete blocks or gypsum board. The finish should be smooth, usually with enamel or epoxy paint.

Prefabricated partitions may be used in packaging areas where flexibility of layout is important. Prefabricated units have also been used in other areas, including sterile suites where panel joints must be given particular attention. Where possible, walls should be flush and projections should be avoided.

- b. Floors. Floor covering should be selected for durability as well as cleanability and resistance to the chemicals with which it is likely to come into contact.
 - i. Terrazzo provides a hard-wearing finish; both tiles and poured-in-place finishes are available. The latter is preferable for manufacturing areas, and if tiles are used, care must be taken to ensure effective sealing between the tiles, which otherwise could become a harboring area of dirt and micro-organisms.
 - ii. Ceramic and vinyl tiles usually are not recommended for production areas. However, if used, the between-tile sealing should be flush and complete.
 - iii. Welded vinyl sheeting provides an even, easy to clean surface. This is not practical for heavy traffic areas, but can be of value in production areas, especially for injectables. Here the lack of joints improves the ease of cleaning and sanitation.

- iv. Epoxy flooring provides a durable and readily cleanable surface. However, the subsurface finish is extremely important.
- c. Ceilings. Suspended ceilings may be provided in office areas, laboratories, toilets, and cafeterias. They usually consist of lay-in acoustical panels of nonbrittle, nonfriable, nonasbestos, and non-combustible material.

Manufacturing areas require a smooth finish, often of seamless plaster or gypsum board. All ceiling fixtures such as light fittings, air outlets and returns, PA system and sprinkler heads should be designed to assure ease of cleaning and to minimize the potential for accumulation of dust.

- d. Services. In the building design, provisions must be made for drains, water, steam, electricity, and other services to allow for ease of maintenance. Access should, ideally, be possible without disruption of activity within the actual rooms provided with the services.

Table 1 provides some guidance on typical finishes for various operations.

(b) Any such building shall have adequate space for the orderly placement of equipment and materials to prevent mix-ups between different components, drug product containers, closures, labeling, in-process materials, or drug products, and to prevent contamination. The flow of components, drug product containers, closures, labeling, in-process materials, and drug prod-

Table 1 Typical Finishes

	Walls	Floors	Ceilings
Warehouse	Painted	Hardened concrete, sealed	
Dispensary	Epoxy	Epoxy or in situ terrazzo	Epoxy
	Coved	Coved	Coved
Solids manufacturing	Epoxy	Epoxy or in situ terrazzo	Epoxy
	Coved	Coved	Coved
Liquids manufacturing	Epoxy	Epoxy or in situ terrazzo	Epoxy
	Coved	Coved	Coved
Solids packaging	Painted	Sealed concrete, terrazzo tile, or vinyl	Suspended ceiling
Liquids packaging (nonsterile)	Epoxy	Epoxy or in situ terrazzo	Epoxy
	Coved	Coved	Coved
Laboratory	Epoxy	Terrazzo tile or epoxy sheet	Suspended ceiling

ucts through the building or buildings shall be designed to prevent contamination.

The requirements of this section involve the design and layout of the facility, which must minimize the possibility of mix-ups or contamination. Sufficient space must be provided to allow adequate separation of adjacent equipment and operations. An example of this includes the spatial separation of packaging lines so that packaging components, bulk product and finished product cannot intermix between lines and that dust or spillage from one line cannot result in contamination of adjacent equipment. For example, a common practice is to introduce a physical barrier between the packaging lines. This need not be a permanent wall, a moveable partition serves the purpose.

The building design should also take into account the flow of materials and people. The movement of people is not addressed in the regulations except for the authorized entry to limited-access areas referenced in 211.28(c). Neither people, equipment, nor work in process should be moved through areas in which other operations are occurring. This requires that areas used for processing should each have separate access from corridors, unless part of a unified operating suite used for one product at a time. When designing a new facility, it is also of value to consider access of those visitors who intend only to have an overview of the facility or its operations. Where possible such visitors should be restricted to personnel corridors having visual access to the operating facilities. This minimizes any potential environmental impact from additional people, limits disruption of operational personnel, and eliminates the need for “dressing-up” to visit.

(c) Operations shall be performed within specifically defined areas of adequate size. There shall be separate or defined areas or other such control systems for the firm’s operations as are necessary to prevent contamination or mixups during the course of the following procedures:

- (1) Receipt, identification, storage, and withholding from use of components, drug product containers, closures, and labeling, pending the appropriate sampling, testing, or examination by the quality control unit before release for manufacturing or packaging;
- (2) Holding rejected components, drug product containers, closures, and labeling before disposition;
- (3) Storage of released components, drug product containers, closures, and labeling;
- (4) Storage of in-process materials;
- (5) Manufacturing and processing operations;
- (6) Packaging and labeling operations;
- (7) Quarantine storage before release of drug products;
- (8) Storage of drug products after release;
- (9) Control and laboratory operations.

This subsection has on occasion been interpreted to mean that separate discrete areas must be provided for each of the listed operations. While there is no dispute with respect to (5), (6), and (9), the other areas are more controversial. However, in the preamble to the regulations it is specifically stated that “separate or defined is not intended necessarily to mean a separate room or partitioned area, if other controls are adequate to prevent mix-ups and contamination.” The Federal Register of February 12, 1991 (56 FR 5671), proposed the inclusion of “as necessary” to qualify the requirement for separate or defined areas. This was to clearly indicate that separate rooms or partitioned areas are not necessary if other controls exist to prevent mix-ups or contamination. This clarification is also present in the preamble to the 1978 final rule. The intent has now been confirmed in the revision (effective February 21, 1995) that added the words “or other control systems.” Facilities and equipment should be designed and operated to minimize the potential for mix-ups or contamination. Where there is reliance on systems, paper or computer, it must be demonstrated that such systems are effective and are followed. As with all key systems, employees must be fully trained in their use and routine audits should be performed. Systems control of storage, and flow of materials and product, can be more effective than physical separation and certainly is more efficient with respect to space utilization and materials handling. Physical movement of materials into and out of quarantine, for example, not only adds cost, but by adding another action, actually increases the potential for error. The further sophistication of bar-coding materials throughout the various plant operations and linking this into a computer materials handling procedure greatly minimizes the chance of unreleased or substandard materials being used inadvertently.

Some companies have found segregation using flexible physical areas to be a satisfactory alternative. For example, in a warehouse, a quarantine area can be designated around the goods simply by roping off the quarantine goods or by placing floor markings. This arrangement allows easy expansion or contraction of the area to meet changing volumes. It should be noted, however, that even physical separation will be ineffective in preventing mix-ups and contamination unless accompanied by adequate support procedures.

While segregation of materials by systems is acceptable, this obviously is inadequate for any materials requiring specific storage conditions—such as low temperature or controlled humidity. In these instances, the required conditions would need to be provided. Receiving areas, where materials are unloaded from delivery transportation, are an access point for airborne contamination such as dirt, dust, insects, vermin, birds, and even engine fumes from the delivery vehicles themselves. Where possible, these access points should be protected by flexible curtains to minimize the gap to the outside when vehicles are unloading; air curtains between the receiving bays and the warehouse proper may also be used

to provide additional protection to the warehouse environment. Insect and rodent traps are usually required.

Sampling, particularly of chemical components, requires separate comment. When containers of components are opened for sampling purposes, the contents are exposed, albeit for short periods, to ambient conditions. It should be demonstrated that normal warehouse conditions do not expose the materials to unacceptable contamination from other components, particulate matter, or microorganisms. Otherwise, separate facilities will need to be provided for sampling. This is addressed in Section 211.80(b).

Traditionally most warehouses for components and finished products have been operated under ambient conditions. Generally, this has been adequate since most pharmaceutical products are sufficiently stable under such conditions and stability data are available to support defined shelf-lives. The prevailing conditions in a warehouse must be monitored and any particularly sensitive products or components should be provided appropriate environments. For relatively stable products, it has been common practice to omit any specific storage conditions on the labeling; it was then assumed that the USP conditions of “room temperature” applied. Recently, some sections of the FDA have been insisting that, in order to obtain approval for new products, defined storage conditions must be stated on the labeling of all products. This has been further complicated by the revision to the USP definition of Controlled Room Temperature, from 15°–30°C to “A temperature maintained thermostatically that encompasses the usual and customary working environment of 20° to 25°C (68° to 77°F); that results in a mean kinetic temperature calculated to be not more than 25°C and that allows for excursions between 15°C and 30°C (59° and 86°F) that are experienced in pharmacies, hospitals and warehouses. Articles may be labeled for storage at ‘controlled room temperature’ or at ‘up to 25°C’ or other wording based on the same mean kinetic temperature.” While it may seem relatively easy to calculate the mean kinetic temperature, in practice this is not so simple. Products remain in facilities for differing lengths of time and it is possible, for example, that a batch of product stored in a warehouse for three summer months may be exposed to a higher mean kinetic temperature than if it were stored for three summer and three fall months. The impracticality of evaluating mean kinetic temperatures for the storage of individual batches is obvious, and it is hoped that a general calculation possibly based on average storage periods will be acceptable. This revised definition, which does not allow excursions above 30°C, is also resulting in many warehouses having to install air conditioning, at considerable expense, to control relatively brief exposure to higher temperatures in summer months.

The issue of labeling is still unresolved. It is considered that the use of the term “controlled room temperature” would be meaningless for certain areas of trade that are not aware of the USP. The more extensive wording of USP–

Controlled Room Temperature is too verbose for most labels and incomprehensible to many areas of the trade. Many companies have retained the old USP definition (15° – 30°C) on their labeling until this is resolved by the FDA.

The subject of stability studies is addressed in more detail in Section 211.66, and since ICH agreement, future stability studies will be performed at $25^{\circ} \pm 2^{\circ}\text{C}$.

The storage period for rejected materials awaiting destruction should be kept as short as possible. These materials take up valuable space and there is always a risk that they may be inadvertently used. Even with the use of a validated storage procedure it may be advisable to maintain physical segregation. FDA investigators have found reference to stored reject materials a useful way to identify production deviations.

Many FDA investigators consider that the presence of reject materials and products demonstrates failure with procedures and consequently is evidence of GMP violations. Rejections of materials could be due to inadequate definition/agreement of specifications, different test methodologies used by the supplier and the customer, nonvalidated analytical methods, nonvalidated production procedures at the supplier resulting in variable quality, use of untrained analysts, or expected data variability around a specification limit. For products, many of the same potential causes apply plus noncompliance with procedures. Frequently an investigator will consider product rejection evidence of an inadequately validated process. Obviously, the cause of any rejection does need to be thoroughly investigated and appropriate corrective action taken and documented.

The degree of separation of individual manufacturing and processing operations will be dependent on the nature of these operations. Raw materials are usually dispensed in an area specifically designed to minimize the potential for mix-ups and for cross-contamination. Scales are separated by partitions and are supplied with dust extraction and sometimes laminar air flow. Where a manufacturing process requires several different pieces of equipment (e.g., blender, granulator, dryer) these may all be contained in one room or suite of rooms. Processes for different products should use completely segregated facilities. Where this is not possible, adequate physical separation should be maintained along with documented evidence to demonstrate the adequacy of the arrangement. This evidence could include data from the analysis of air samples which confirms that the potential for cross-contamination is negligible. However, where such arrangements are necessary it would be advisable to provide separate facilities for any particularly potent or sensitive products or manufacture in campaigns.

Packaging and labeling operations are usually kept separate from manufacturing. Even when a highly automated process is used, and packaging immediately follows manufacturing, the packaging is usually performed in an adjacent area.

The need to provide physical barriers between packaging lines has already been mentioned. Particular attention needs to be paid to the on-line storage of bulk product, labeling, and filled but unlabeled containers. During packaging operations it is not uncommon for individual pieces of line equipment to break down. Under these circumstances it may be economically viable to continue the operation and to accumulate part-packaged product until the effective unit is repaired. When the labeling unit breaks down, special care must be taken to ensure that unlabeled containers do not get onto another line, or even intermixed with a different batch of the same product. Where possible, accumulation tables should be an integral part of a packaging line, thereby enabling short down-times on equipment to be handled without the need to remove part-packaged product from the line. Protracted breakdown of labeling equipment may on occasion result in amounts of unlabeled product in excess of the capacity of accumulation tables. Also, some processes are designed to produce filled unlabeled product. This includes sterile products such as ampoules and vials which are labeled outside of the sterile suite. Obviously, in such situations great care must be taken to prevent mix-ups. When labeling is to be performed later, security can be enhanced by holding the unlabeled product in sealed or locked containers (see also [Chapter 8](#)).

The requirement of separate areas for control and laboratory operations does not preclude the use of in-process testing within the manufacturing and packaging areas. However, the environmental conditions in these areas must be suitable for the proper operation of the equipment and performance of the testing. In some instances it may be necessary to site in-process test equipment in designated areas or rooms within the manufacturing or packaging facilities.

- (c) (10) Aseptic processing, which includes as appropriate:
 - (i) Floors, walls, and ceilings of smooth, hard surfaces that are easily cleanable;
 - (ii) Temperature and humidity controls;
 - (iii) An air supply filtered through high-efficiency particulate air filters under positive pressure, regardless of whether flow is laminar or non-laminar;
 - (iv) A system for monitoring environmental conditions;
 - (v) A system for cleaning and disinfecting the room and equipment to produce aseptic conditions;
 - (vi) A system for maintaining any equipment used to control the aseptic conditions.

This subsection emphasizes the special requirements associated with aseptic processing. Some companies also apply aseptic processing techniques during the production of terminally sterilized products. In these cases compliance with the regulations is not mandatory, although it does make good sense. The absence

of a terminal sterilization process and the relative ineffectiveness of end product sterility testing place a critical reliance on the environmental conditions associated with aseptic processing. Recognizing the importance of aseptic processing in the production of injections, the FDA issued a "Guideline on Sterile Drug Products Produced by Aseptic Processing" in 1987. However, with respect to facilities, the guide provides guidance only on air quality, air flow, and pressure differentials. There is no information on surface finishes.

Floors, walls, and ceilings in sterile suites are subject to intensive and frequent cleaning and sanitization; they must be composed of smooth, hard surfaces with a minimum of joints. Additionally, they should be resistant to abrasion, not shed particles, be free from holes, crevices, and cracks, be sufficiently flexible to accommodate building strains, and be impervious to water and cleaning and sanitization solutions. Regular examinations should be performed to identify and repair any cracks in the surfaces or around service fittings and windows. Critical rooms such as those for filling of final containers should preferably have windows to allow supervision without the necessity for access. All service fittings should be flush with surrounding surfaces for ease of cleaning and sanitization.

Temperature and humidity need to be controlled primarily for the comfort of operators. The gowning requirements to minimize the potential for microbial contamination from operators are rather stringent and can easily cause personal discomfort, which could in turn adversely impact on the aseptic processing. Conditions in the order of 68°F and 45% relative humidity (RH) have been found to be suitable.

The most critical factor in aseptic processing is the microbial and nonviable particulate condition of the air. This air is provided by way of high-efficiency particulate air filters (HEPA) and the quality of the air is adjusted to meet the varying needs of the different processing areas. At the most vulnerable points where sterilized containers and closures are exposed and filling and sealing operations occur, air is supplied with less than 100 particles of 0.5 micron or larger (Class 100) and with not more than one colony-forming organism per 10 cubic feet. Airflows of about 90 feet per minute are recommended. These sensitive areas should also have a positive pressure differential relative to adjoining areas of at least 0.05 inch of water. This usually requires a filter with a 99.97% DOP efficiency. Within aseptic processing rooms it is usual to additionally incorporate laminar flow services over and around these most sensitive areas. These laminar flow facilities should direct the filtered air in such a way that particulate matter from equipment or personnel is directed away from the sensitive points.

Other areas associated with aseptic processing but where the key sterile materials are not exposed do not require such rigorous conditions. This includes solution compounding, equipment and component preparation, personnel changing and gowning. For these, air with not more than 100,000 particles of 0.5 mi-

crons or larger (Class 100,000) and not more than 25 colony-forming organisms per 10 cubic feet is acceptable. Air flow should be sufficient to provide 20 changes per hour and positive pressure differentials between adjacent areas.

Such heavy emphasis on air quality necessitates appropriate systems and procedures for monitoring. This will include evaluation of pressure differentials between rooms, particulate levels (viable and nonviable) and also temperature and humidity.

Air-pressure differentials should be monitored automatically and audible or visual warning alarms are an added advantage. The number of rooms inter-linked in a sterile suite makes the balancing of air-pressure differentials very difficult. Movement of people and materials, involving opening and closing of doors, adds to the complexity. Computer control can provide a more rapid response to these changing conditions. HEPA filters must be tested at regular intervals for the presence of leaks; such leaks would also be likely to affect pressure differentials. Particulate levels are usually monitored during each work shift or part shift when operators leave and return; air sampling devices are most commonly used since they do provide a quantitative measure of the volume of air sampled. However, for microbial evaluation settle plates can also be of value since they provide a measure of the microbial impact over a more protracted period—say 30 minutes.

Cleaning and disinfection of aseptic facilities and equipment are of obvious importance, especially in the critical areas. Procedures must be validated with respect to both removal of previous product and to demonstrate effective disinfection. Residual amounts of any cleaning or disinfectant agents should be at an acceptably low level. In order to minimize the possibility of microbial resistance, the disinfectant should be changed periodically. After cleaning and disinfecting, rooms and equipment must be maintained in such a manner that these conditions are not impaired.

For certain pieces of equipment a “clean-in-place” procedure is most effective. This is particularly valuable with tanks and pipelines where access or dismantling may be difficult. The procedure basically consists of applying sequential wash, sanitization and flush cycles to the assembled equipment. Sanitization is often accomplished with high-pressure steam.

Having established suitable conditions for aseptic processing, it is necessary to have a defined maintenance program for equipment and facilities. In addition to the servicing of HVAC equipment and checking of ducts, filters and service ports for leaks, the physical condition of walls, floors and ceilings should be monitored. Slight shifts in building position, which are not uncommon, can result in cracks, which then need to be repaired.

The environmental conditions are essentially established by flushing the area with high-quality air. Any disruption in this flushing process will affect

pressure differentials and possibly adversely affect the conditions. Consequently the provision of auxiliary generating capacity to maintain essential air-handling equipment can be a valuable asset. This equipment should switch on automatically in the event of a power failure and will allow completion of ongoing sensitive operations and maintain the environment until normal power is restored. Where such auxiliary power is not available, aseptic operations should cease immediately if there is a power failure and restarting will not be possible until the reestablishment of the defined condition has been confirmed.

The industry is now beginning to introduce barrier technology systems as a means of enhancing levels of sterility assurance and, for new facilities, reducing costs. Two main variations exist—barrier isolation systems, which protect the product from the operators and the external environment, and barrier containment, which additionally protects the operator from the product. Barrier containment is frequently used when handling high hazard or cytotoxic agents. Both systems contain the aseptic operating environment within a closed system with no direct access to operators. Access is via glove ports with sterilized components being fed directly from a sterilizing/depyrogenizing tunnel or after batch processing via a rapid transfer port. Clean and sterilize in place procedures are required.

The space required to be maintained at a Class 100 level is significantly less than for traditional aseptic rooms and this can have important cost implications. The overall facility can be smaller, the Class 100 space costs less than one quarter the cost of clean space, gowning areas can be eliminated. Additional benefits include more consistent assurance of sterility since the microbial and nonviable particulate content of the processing environment is constant—no operator involvement and more comfortable working conditions for employees. The actual level of sterility assurance should be greatly enhanced—possibly from 1×10^{-3} to 10^{-5} or 10^{-6} .

(d) Operations relating to the manufacture, processing and packing of penicillin shall be performed in facilities separate from those used for other drug products for human use.

This is the first of several portions of the regulations that pertain specifically to the production of products containing penicillin [see also Sections 211.46(d) and 211.176].

The FDA holds that there is a possibility of trace amounts of penicillin being released even under well-controlled conditions. Separate equipment for use only for products containing penicillin is required. The isolation of penicillin production operations from operations for nonpenicillin products is required. Separation can be achieved even within a single building by effectively isolating the

penicillin operation from other operations. Separation by geographical distance or the construction of a separate building is not required, but may be the preferred economic alternative.

§211.44 LIGHTING

Adequate lighting shall be provided in all areas.

In order to meet lighting requirements, it is necessary for the manufacturer to define the term “adequate.” This may be done by defining the amount of light (lux or foot-candles) reaching the working surface for each area involved in the production of pharmaceuticals. Public standards exist for some types of work. Normally, a range of 30–50 foot-candles ensures worker comfort and ability to perform efficiently and effectively; however, 100 foot-candles may be needed in some areas, as well as special lighting for some operations, such as inspection of filled vials. Once the light levels have been defined, it is necessary that they be measured periodically and the results recorded. The specifications should call either for replacement of light sources when some level above the established minimum has been reached or, alternatively, routine replacements of light sources on some schedule that has been shown adequate to ensure that light levels do not drop below the established minimum.

§211.46 VENTILATION, AIR FILTRATION, AIR HEATING AND COOLING

- (a) Adequate ventilation shall be provided.
- (b) Equipment for adequate control over air pressure, microorganisms, dust, humidity, and temperature shall be provided when appropriate for the manufacture, processing, packing, or holding of a drug product.
- (c) Air filtration systems, including prefilters and particulate matter air filters, shall be used when appropriate on air supplies to production areas. If air is recirculated to production areas, measures shall be taken to control recirculation of dust from production. In areas where air contamination occurs during production, there shall be adequate exhaust systems or other systems adequate to control contaminants.
- (d) Air-handling systems for the manufacture, processing and packing of penicillin shall be completely separate from those for other drug products for human use.

The regulations provide minimal guidance by stating that ventilation should be adequate. It is then up to the producer to demonstrate adequacy with respect

to the operations being performed. The conditions necessary for aseptic processing have already been described [Section 211.42(c)(10)].

Air-handling systems should consider the following factors:

1. Placement of air inlet and outlet ports. These should be sited to minimize the entry of airborne particulates or odors from the surrounding areas. Outlets should not be sited near inlets.
2. Where recirculation of air is acceptable, adequate precautions must be taken to ensure that particulates from a processing area are removed. This will usually require an alarm system or an automatic cutoff in the event that a filter develops a hole. Dust extraction systems should be provided, where appropriate, to further minimize this potential problem.
3. The degree of filtration and the air volumes should be matched to the operations involved.
4. Temperature and humidity conditions should provide personnel comfort—which will enhance employee performance.
5. Where differential pressures are required between adjacent areas, suitable monitoring equipment must be provided. For example, solids manufacturing areas are usually maintained at a negative pressure in relation to adjacent rooms and corridors in order to minimize the possibility of dust migration to these other areas.
6. The siting of final air filters close to each room being serviced eliminates concerns regarding the possibility of small leaks in the air duct system. Air usually enters rooms near the ceiling and leaves from the opposite side near the floor.

As with all systems, operating requirements should be defined and monitored at appropriate frequency to ensure compliance. If conditions are shown to have fallen below the required standards, it may be necessary to more thoroughly evaluate any products that were produced during the period in question.

It is important to monitor filters to ensure proper operation. After initial mounting and testing with a smoke generator of defined particle size range, the use of a differential manometer to monitor pressure drop across the filter gives warning of both breaks in the filter and buildup of retained particulates necessitating filter replacements. A specification of maximum permissible pressure drop before replacement should be defined.

As indicated previously for sterile areas, computer control of HVAC systems is more likely to allow the delicate balancing of the various air pressures, air flows, temperature, and humidity. When this is expanded to the entire plant systems, the computer control can additionally optimize energy utilization, thereby reducing costs.

The regulations also make specific reference to the handling of penicillin products [211.46(d)]. Not only shall such operations be performed in separate facilities from those for other drug products for human use [211.42(d)], they must also have separate air handling systems.

§211.48 PLUMBING

(a) Potable water shall be supplied under continuous positive pressure in a plumbing system free of defects that could contribute contamination to any drug product. Potable water shall meet the standards prescribed in the Environmental Protection Agency's Primary Drinking Water Regulations set forth in 40 CFR Part 141. Water not meeting such standards shall not be permitted in the potable water system.

(b) Drains shall be of adequate size and, where connected directly to a sewer, shall be provided with an air break or other mechanical device to prevent back-siphonage.

The Public Health Service Drinking Water Standards are now administered by the Environmental Protection Agency (EPA). The standard is somewhat variable in that the frequency of examination of the water is dependent on the size of the population served. This leads to some uncertainty in water quality if potable water becomes part of a pharmaceutical product. This problem does not arise for products of the official compendia [*United States Pharmacopeia* (USP) and *National Formulary* (NF)], for which purified water is always required. The text of the drinking water standards is found in 40 CFR 141.

The FDA usually will not inquire into whether the potable water does meet the standard, if the manufacturer connects the potable waterline to a public supply that meets the standard. A quality control problem arises, however, in that the public supply ensures the quality only to the edge of the manufacturer's property, and even then tests, usually, only at the central reservoir. The water can lose quality in transmission through the public piping system and, of course, through the manufacturer's system. The prudent manufacturer will test potable water periodically. If potable water is obtained from wells under the control of the manufacturer, periodic testing is mandatory.

Where it is necessary to provide on-site potable water storage, an automatic chlorination system should be installed, usually at 2–3 ppm.

Drains, particularly those in production areas, can be a potential source of microbial hazard. The requirement to include an air break between drain and sewer is an attempt to minimize this by eliminating the chance of back-siphonage. Drains should also be regularly disinfected.

§211.50 SEWAGE AND REFUSE

Sewage, trash, and other refuse in and from the building and immediate premises shall be disposed of in a safe and sanitary manner.

A pharmaceutical plant may consider disposal in several different ways:

1. **Product disposal.** Any product requiring disposal should initially be separated from its packaging if appropriate. For example, any product to be disposed of in an approved landfill site should not be left in impermeable glass, plastic, or other containers which would significantly delay destruction. Tipping of product to bulk or crushing would be viable pretreatments. There are risks associated with the destruction of products—potential for the product to get diverted, legitimately or otherwise, during the disposal sequence and contamination of groundwater. Disposal procedures should involve agents with a proven record of dealing with such sensitive materials or the use of company personnel to accompany the material from plant to disposal. Ideally, incineration procedures have preference over landfill. Where incineration is used, product in plastic or other flammable packaging may not need to be returned to bulk.

2. **Printed packaging disposal.** The disposal of printed packaging components including labels, inserts, and cartons poses no health risk. However, ineffective disposal, such as into public landfill, can give rise to public concern that product may be associated with the packaging. Such materials should preferably be incinerated.

3. **General trash and sewage.** Normal local services will usually be adequate for trash and sewage. However, internal procedures should be sufficiently rigorous and monitored, to ensure that product and packaging waste does not get intermixed. Containers used within the plant to accumulate waste materials should be clearly marked to denote their designated use.

§211.52 WASHING AND TOILET FACILITIES

Adequate washing facilities shall be provided, including hot and cold water, soap or detergent, air driers or single-service towels, and clean toilet facilities easily accessible to working areas.

In addition to GMP regulations, Occupational Safety & Health Administration (OSHA) regulations impact on washing and toilet facilities (see 29 CFR 1019.141). These require toilet rooms to be separate for each sex except where individual locked toilet rooms are available and also define the minimum number of water closets based on the number of users. The legal requirements of Good Manufacturing Practices specify minimum facilities for personnel. Management

concern with employee morale, and extra measures to ensure minimum probability of contamination, suggest additional emphasis and activities.

1. Eating facilities:
 - a. Eating and drinking are permitted only in separate eating facilities well segregated from all production areas [see also 29 CFR 1910.141(s)(g)(2)]. Smoking is permitted only where an adequate disposal device is provided and apart from production areas.
 - b. Prominent signs indicating these rules are posted at entrances to production areas.
 - c. Enforcement procedures against violators are taken by management.
 - d. Permanent facilities for breaks and people bringing lunches are required. Cafeterias serving hot meals are ideal to reduce the amount of food, a potential contamination source, being brought into the plant.
2. For production and materials processing areas:
 - a. Drinking, eating, smoking, tobacco chewing, and expectoration are prohibited.
 - b. Tissues and closed disposal containers are readily available.
3. Lavatories and lockers:
 - a. Adequate in number for the number of personnel employed.
 - b. Conveniently located to all areas.
 - c. Hot shower facilities are provided [see also 29 CFR 1910.141-(s)(d)(d)].
 - d. Disinfectant soaps are utilized.
 - e. Adequate ash and waste receptacles are provided.
 - f. Periodic cleaning of the area during each shift with logging of times and conditions is mandatory.
 - g. Complete cleaning with cleansing and disinfectant agents daily. Follow-up inspection by supervisory personnel is logged.
 - h. Specific rest areas for female employees are provided.
 - i. Eating and drinking are not permitted. Foods and beverages for meals and breaks may be stored only in lockers and then removed to a separate eating area.
 - j. Areas separated from all aseptic spaces by an air lock.

§211.56 SANITATION

(a) Any building used in the manufacture, processing, packing, or holding of a drug product shall be maintained in a clean and sanitary condition. Any

such building shall be free of infestation by rodents, birds, insects and other vermin (other than laboratory animals). Trash and organic waste matter shall be held and disposed of in a timely and sanitary manner.

(b) There shall be written procedures assigning responsibility for sanitation and describing in sufficient detail the cleaning schedules, methods, equipment, and materials to be used in cleaning the buildings and facilities; such written procedures shall be followed.

(c) There shall be written procedures for use of suitable rodenticides, insecticides, fungicides, fumigating agents and cleaning and sanitizing agents. Such written procedures shall be designed to prevent the contamination of equipment, components, drug product containers, closures, packaging, labeling materials, or drug products and shall be followed. Rodenticides, insecticides and fungicides shall not be used unless registered and used in accordance with the Federal Insecticide, Fungicide, and Rodenticide Act (7 U.S.C. 135).

(d) Sanitation procedures shall apply to work performed by contractors or temporary employees as well as work performed by full-time employees during the ordinary course of operations.

This requirement relates to the availability of effective cleaning and sanitation programs and confirmation that they have been followed. No details are given, nor should they be, on how to achieve the desired conditions. Cleaning and sanitation programs should be adjusted to meet the specific needs of each facility. In addition to the cleaning of floors, walls, and ceilings, there should be attention to dust extraction and air input systems. Duct work, especially for dust extraction systems, can become a potential explosion hazard if dust is allowed to accumulate.

Cleaning procedures should be written in sufficient detail with respect to materials, equipment, process, and frequency that they are unambiguous. Where appropriate, data should be accumulated to confirm the adequacy of the cleaning procedure.

The total elimination of rodents, birds, and insects is virtually impossible and the regulations do refer to freedom from "infestation." The use of rodenticides, fungicides, fumigating agents, and other techniques should be combined with good hygienic practices. Spilled materials, such as sugar, that might attract creatures should immediately be eliminated. Holes in buildings that could provide additional means of access should be blocked.

Where traps and other lethal techniques are used, there should be frequent examination and removal of "corpses," which could in time become a source of further contamination. If these traps consistently yield results, attempts should be made to identify and eliminate the source of the problem.

Frequently rodenticide and other treatments are contracted out. As with any contracted service, the company must assure that the procedures used are viable, achieve the desired results, and that they are followed.

§211.58 MAINTENANCE

Any building used in the manufacture, processing, packing, or holding of a drug product shall be maintained in a good state of repair.

Deterioration of buildings not only presents a poor image of the facility, it can also impact on product quality. Cracks and holes in walls, floors, or ceilings can provide access for insects, rodents, birds, dirt, or microorganisms. They can also hinder cleaning and sanitation, thereby increasing the potential for cross-contamination or microbial multiplication. Floor cracks can also become a safety hazard for people or even dislodge materials from trucks.

The ingress of water from roof leaks can cause significant damage to materials and equipment, give rise to electrical failures and fires and result in damage to the basic structure of the building. Additionally, holes in the roof or near the tops of buildings provide ready access to birds, which may then be encouraged to nest within the building.

BUILDINGS AND FACILITIES

Damage to insulation or pipes and duct work will detract from the basic purpose of such insulation. It may also result in freezing and eventual leakage of pipes and in the shedding of insulation material into product and equipment.

Light fittings need regular cleaning to remove any accumulated dust, which can act both as a potential source of contamination and reduce light intensity.

Where the proper correction of building deficiencies requires shut-down of the area, it may be necessary to resort to temporary repair until adequate time can be made to enact a permanent repair. Building inspection and maintenance programs should be defined in writing and a record kept confirming compliance and referencing any repairs performed.

This regulation specifically refers to buildings, while Section 211.67 relates to equipment. This appears to ignore the maintenance of services, some of which are included in other sections of Subpart C, but without reference to maintenance. Clearly services can impact directly on processing and product quality and they must undergo routine maintenance. Essential services will include HVAC, water (all types), steam, vacuum, compressed air and other gases, electricity, dust extraction, product/material pipelines, drainage, and sprinkler system.

GENERAL OBSERVATIONS

Building new or renovating present pharmaceutical or related manufacturing facilities represents special problems and the need for special expertise. A number

of architectural and engineering firms take on the majority of such projects. They should be selected with great care and ongoing review of the project, preferably by outside experts as well as the internal team, should be the rule.

Because this author's experience amounts mainly to some situations where some ultimate dissatisfaction has led to legal review of the potential for recovery, we are presenting additionally a series of observations that were developed in such retrospective.

First, bear in mind that the usual contract between the owner and the architect is a version of a "Standard Form of Agreement Between the Owner and the Architect" prepared by the American Institute of Architects. It contemplates arbitration, rather than recourse to the court system, in case of a disagreement as to its terms or its performance. Therefore, competent and experienced legal advice prior to entry into the contract is required. Not all the boilerplate of the standard agreement need be accepted, and riders can be added to afford greater protection to the owner. In larger projects a contractual relationship to the Production Manager is likewise important to define. There are the agreements with Contractor and Subcontractors, agreements that must contemplate a schedule process that is reasonably enforceable by the Production Managers and the Owner's team. It is a major undertaking that in the last instance needs in a timely manner to meet the requirements of the federal and state and local agencies involved. People involved in such a project by the owner, I recommend be absolved from other responsibilities, but they should have the quality control "savvy" that the average architect and engineer may not possess.

The Project Manager will usually be supported on a large project by a project architect, a project mechanical services engineer, project electrical engineer, project structural engineer, project civil engineer, and project landscape architect.

When we recall the nature of later complaints, we urge a careful and extensive reading of the foregoing material in this chapter. Legal recourse is limited by the expertise of those who would provide it. It is limited by time as well, since a claim based on negligence of those contracted with must usually be brought within 2 years from actual or constructive discovery of the harm. A Breach of Contract Claim has a 4-year statute of limitations from the time of breach.

Typical claims: "unbalanced" air systems, undersized exhaust fans, problems with heat exchangers, insufficient light levels, pressure monitoring problems, seal dampers not meeting specifications, inadequate roof or room drains, condensate problems, undersized electrical systems, improper laminar flow hoods, flawed water supply, inadequate geologic surveys, etc., are some we recall.

Obviously intimate, close supervision must be accomplished by knowledgeable employees and agents of the owner. Otherwise that requisite expansion, the new buildings may become a large drain swollen by lost time and financial

resources. And, of course, failures in planning, in equipment and personnel handicapped by these result in the FDA citations following.

EXAMPLES OF OBSERVATIONS FROM FDA 483 CITATIONS

1. The sterility test room was not designed and constructed to facilitate cleaning and disinfection.
2. The HVAC and dust collection systems are not validated.
3. The direction of air flow is not monitored in the manufacturing rooms.
4. There are no approved procedures for maintaining the HVAC and dust control systems throughout the plant.
5. The WFI system is not designed in a manner to minimize microbial contamination and endotoxin load. For example, in the past year there have been ten incidents of WFI samples that exceeded specifications for microbial contamination.
6. The written procedures covering pest control within the buildings are not signed or dated by the personnel who prepared and authorized them.
7. Inspection of the reverse osmosis water system revealed dead legs, which are potential sites for microorganisms to lodge, multiply, and enter the effluent.
8. There are no temperature or humidity specifications for the area.
9. Sensors for monitoring warehouse temperature have not been calibrated since their installation three years ago.
10. Air recirculated in the compressing area has never been tested for particulate matter. Validation of the air handling system is inadequate—samples for cross contamination were collected from only . . . cubicles in the compressing area.

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5

Equipment (Subpart D)

§211.63 EQUIPMENT DESIGN, SIZE, AND LOCATION

Equipment used in the manufacture, processing, packing, or holding of a drug product shall be of appropriate design, adequate size, and suitably located to facilitate operations for its intended use and for its cleaning and maintenance.

The effectiveness of equipment, like the quality of a product, starts at the design stage. Most pharmaceutical companies are not directly involved with the designs and construction of equipment but they can contribute indirectly. They can, and do, provide information on requirements and feedback on existing equipment.

When evaluating alternate types or makes of equipment, several parameters need to be considered:

1. Operating criteria are adequate for the process—size, speed, effectiveness (of, say, a mixer).
2. Availability of spares and servicing. This can result in using different makes of equipment in different parts of the world.
3. Maintenance. The frequency and ease of maintenance will significantly impact on productivity and even quality. Equipment breakdown during processing could adversely affect quality. Included in the maintenance

evaluation should be the cleanability of the equipment. This will involve accessibility to the parts needing to be cleaned and the relative ease of disassembly and reassembly.

4. Environmental issues. Does the equipment disseminate dust, with the potential for contaminating other products or making it necessary for operators to wear additional protective clothing and facilities to be cleaned more frequently? The possible impact of noise and energy use and dissipation should be considered.
5. Construction materials and design (see §211.65 below).
6. Availability of process controls such as automatic weight adjustment on tablet presses and temperature recorders on ovens. Although initially more expensive they could prove to be very economic overall by providing more consistent product quality and better records.
7. Cost. A comprehensive cost should, if possible, be compiled which will include the base price plus any additional costs associated with points 2–4 above.
8. Availability of design and maintenance manuals from the supplier that are important for validation/qualification and maintenance programs.

New equipment should not be used for commercial production until it has been qualified and the process in which it is to be used has been validated; this applies equally to laboratory and other test equipment. Qualification of equipment is reviewed in Chapter 7 under the heading of Process Validation. All equipment should be appropriately identified, usually with a unique number, to allow reference in maintenance programs and in batch records (see also §211.105(a)).

§211.65 EQUIPMENT CONSTRUCTION

(a) Equipment shall be constructed so that surfaces that contact components, in-process materials, or drug products shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements.

Compliance with this subsection requires the manufacturer to determine which drug products and materials are to be processed in the equipment and where contact between materials and machinery occurs. Since many of the surfaces of processing equipment are either stainless steel or glass this is not too great a task. However, stainless steel is not totally inert and care should be exercised in choosing the grade—note that distilled water is very corrosive and requires 316 grade, which should then be passivated, usually with 15–30% nitric acid. Evaluation of potential interactions will include introduction of unacceptable extractives from the equipment into the product, alteration of the physical

or chemical properties of the product, and introduction of particulates from abrasion of surfaces.

(b) Any substances required for operation, such as lubricants or coolants, shall not come into contact with components, drug product containers, closures, in-process materials, or drug products so as to alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements.

This requirement affects the design, construction, and placement of manufacturing equipment. Motors, drive belts, gears, and other potential sources of lubricant contamination should be located away from vessel or package openings that could result in product contamination. For equipment where this is not possible, such as some mixers and tablet and encapsulating machines, lubrication needs to be controlled and monitored; buildup of lubricant and powdered product should be regularly removed and lubricants should be of food grade.

Gaskets and other connecting surfaces should be monitored to ensure they don't break down, thereby allowing environmental contamination or gasket particles into the product.

§211.67 EQUIPMENT CLEANING AND MAINTENANCE

(a) Equipment and utensils shall be cleaned, maintained, and sanitized at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements.

(b) Written procedures shall be established and followed for cleaning and maintenance of equipment, including utensils, used in the manufacture, processing, packing, or holding of a drug product. These procedures shall include, but are not necessarily limited to, the following:

(1) Assignment of responsibility for cleaning and maintaining equipment;

(2) Maintenance and cleaning schedules, including, where appropriate, sanitizing schedules;

(3) A description in sufficient detail of the methods, equipment, and materials used in cleaning and maintenance operations, and the methods of disassembling and reassembling equipment as necessary to assure proper cleaning and maintenance;

(4) Removal or obliteration of previous batch identification;

(5) Protection of clean equipment from contamination prior to use;

(6) Inspection of equipment for cleanliness immediately before use.

(c) Records shall be kept of maintenance, cleaning, sanitizing, and inspection as specified in §211.180 and §211.182.

It is of interest to note that (a) identifies two reasons for cleaning, maintenance and sanitation. First, to prevent contamination from materials previously utilizing the equipment. The second reason is an acknowledgment that inadequate cleaning or maintenance may cause equipment to malfunction or break down and that this could have an adverse effect on the process or product. For example, if a process required stirring for 30 minutes at 60°C and the stirrer broke down, it is likely that the exposure to heat could exceed 30 minutes by the time the stirrer was repaired or replaced.

The regulations require written procedures for cleaning, maintenance, and where appropriate, sanitation, but do not define who should approve these procedures. It would seem logical that the engineering department should approve the maintenance programs while cleaning and sanitation should be approved by quality control. The methods used for cleaning and sanitation should be supported by appropriate validation. This will confirm that the procedures do effectively remove the previous materials or reduce them to acceptable levels.

The importance of cleaning was further emphasized by the publication of the FDA “Guide to Inspections of Validation of Cleaning Procedures” in July 1993. This guide suggests that FDA investigators evaluate key areas including:

1. Availability of approved validation protocols.
2. Approved validation reports.
3. Equipment design and cleanability.
4. Defined, reproducible cleaning procedures that address difficult-to-clean areas. Different cleaning procedures are acceptable between batches of the same product and between batches of different products. For manual cleaning operations, it is essential that sufficient detail is provided to give a high level of assurance that the procedure will be performed essentially the same way by different operators. For example, “wash with water” would be totally unacceptable. Repeat cleaning until test results are acceptable is considered indicative of a nonvalidated process.
5. Time scales between use and cleaning and between cleaning and reuse.
6. Operator training.
7. Specificity and sensitivity of analytical methods—which must be validated, along with recovery levels. Although specific analytical methods are most frequently used, another alternative is a general method such as total organic carbon, which will evaluate all carbon-containing materials.
8. Sampling methods.

(a) Swab testing of measured areas of surface. The swab is then extracted with an appropriate solvent and the level of extractive quantified. Extrapolation of the amount of residue obtained from the swab

to the total surface area of the equipment provides a measure of the total residue—which is potentially capable of being transferred to the next product. An advantage of this method is that areas that are hard to clean may be swabbed (provided they are accessible). One disadvantage is that some areas may not be accessible. During the analytical method validation, it is important to demonstrate that components in the swab material do not interfere with the results.

(b) Solvent rinse. After cleaning, the entire equipment surfaces are flushed or rinsed with a solvent in which the materials being evaluated are soluble. By calculating the amount of solvent likely to be left in the equipment, which may later evaporate (or be carried over), it is possible to calculate residue levels. This method has the advantage that it can be used for difficult-to-reach equipment parts such as valves and pipework. It is important to demonstrate that residual materials are not adsorbed onto surfaces thereby giving a low value.

The FDA does not favor this approach and uses a “dirty pot” analogy—you don’t check whether a dirty pot has been cleaned by examining the wash water. However, it would seem that the rinse solvent approach does have merit provided it is linked to confirmation of nonadsorption and visual examination.

(c) Placebo flush. For solid dosage processing it may be possible to flush the equipment system with placebo or excipient material such as lactose. Testing of the placebo for residues of the previous product will provide the required data. This approach is not favored by the FDA, which argues that homogeneity cannot be guaranteed.

(d) Evaluation of next product. In theory this is possibly the most meaningful way to evaluate carryover. However, it does have problems. The analytical methodology to detect traces of product A in product B is complex—especially if every combination of A and B needs to be evaluated and validated. The carryover may not be homogeneous. The method can provide some useful data, but again this is not included in the FDA Guide.

(e) Visual examination—should always be performed and there are now ways available to perform this in pipework.

9. Acceptable residue limits. At one stage some FDA investigators were proposing “nondetectable” as the only accepted limit. This was both illogical and unnecessary. Analytical methodology is becoming so sensitive that detection levels in parts per million or billion are possible. The practical difficulties associated with the achievement of such low residue levels are time-consuming and costly. A more practical approach is to calculate levels for each material that are below the range of therapeutic effect. The literature includes such alternatives as 1/100

and 1/1000 of the minimum therapeutic dose of A carried over into the maximum therapeutic dose of B. For highly potent compounds or sensitizing products, tighter limits may be required. For cleaning agents such as detergents a more generic approach is sometimes used with acceptance levels of NMT 10 ppm. These approaches appear to be scientifically sound since very few ingredients of pharmaceutical formulations are physiologically active at these low levels. The FDA Guide does accept that there is likely to be considerable variability between products and companies, and it encourages investigators to evaluate the scientific logic of a company's approach. The guide does, however, make reference to 1/1000 therapeutic dose, 10 ppm, and no visual residues.

Whatever approach is used by a company, there may be some exceptions—where the analytical methodology is not available to detect the very low levels associated with the calculated acceptable residue levels. In these instances, specific individual evaluations of possible therapeutic impact of higher levels need to be performed.

Once a cleaning method is validated, it should be followed. As indicated previously, it is permitted to process consecutive lots of the same product with the same equipment for a reasonable period without complete cleaning. A time limit should be established for this practice to assure there is no unacceptable buildup of residues or multiplication of microorganisms.

The amount of work required to evaluate cleaning effectiveness for every material/formulation in every type of equipment is enormous, especially if new analytical methods have to be developed and validated. However, it may be acceptable to apply a scientifically based matrix approach along the following lines:

1. Identify the different pieces of equipment used in the production operations
2. Identify the least soluble ingredients used in formulations and validate cleaning procedures for these for different pieces of equipment
3. Identify areas of equipment that may be difficult to clean, based on professional judgment. During validation studies this equipment should be disassembled if possible to confirm cleaning. If not clean, alternative cleaning procedures may need to be developed or routinely disassemble the equipment for cleaning or obtain different equipment
4. Identify materials that adsorb onto equipment surfaces. Use swab testing for evaluation and use special cleaning procedures/agents.

Once validated, it may still be advisable to reconfirm cleaning effectiveness from time to time. For manual processes this is essential until sufficient data has been generated to confirm the reproducibility of the cleaning procedure.

More recently the FDA has begun to challenge cleaning procedures for laboratory equipment, and companies should be reexamining these procedures and the supporting data.

Production equipment is to be status labeled (§211.105(a)). Consequently it is important that any labeling which relates to the previous process is removed as part of the overall process of preparing equipment for the next product or batch.

Once equipment has been cleaned it is necessary that it remains clean until use. This may require some degree of protection or covering plus an inspection immediately prior to use. Batch records should include a note of this inspection which is both a check of the status labeling, confirming that equipment has been cleaned, and visual check that it looks clean. To eliminate the need for these confirmatory checks it has been suggested that cleaning and sanitation should be delayed until immediately prior to the next production run. This is unacceptable since it could be more difficult to remove “caked-on” material than fresh material, also microbial growth in the presence of organic material is likely to be accelerated. Where microbial cleanliness is important damp equipment should not be left for any significant length of time before use—it may need to be dried or rinsed prior to use.

Where appropriate clean-in-place techniques may be applied; these have the advantage of not requiring the time-consuming stages of disassembly and reassembly. The method has especial applicability to pipelines and can even be adapted to sterilize in-place.

Where dedusting procedures are utilized, these should involve vacuum rather than pressure; the latter simply spreads contamination.

The importance of the plant maintenance program is often underestimated with respect to its potential impact on product quality. The main emphasis for maintenance programs is to minimize the potential for breakdowns and to optimize production cycle times. This emphasis is important. However, poor maintenance can also result in equipment not functioning as intended, with consequent impact on processing and quality. Inadequate maintenance can also enhance the potential for lubricant leakage, wear on bearings and other equipment components, which could disgorge metal into the product, and difficult-to-remove buildup of residues, which could later dislodge. Many companies include metal-detecting equipment as an integral part of the manufacturing of solid dosage forms.

§211.68 AUTOMATIC, MECHANICAL, AND ELECTRONIC EQUIPMENT

- (a) Automatic, mechanical, or electronic equipment or other types of equipment, including computers, or related systems that will perform a function

satisfactorily, may be used in the manufacture, processing, packing, and holding of a drug product. If such equipment is so used, it shall be routinely calibrated, inspected or checked according to a written program designed to assure proper performance. Written records of those calibration checks and inspections shall be maintained.

(b) Appropriate controls shall be exercised over computer or related systems to assure that changes in master production and control records or other records are instituted only by authorized personnel. Input to and output from the computer or related system of formulas or other records or data shall be checked for accuracy. The degree and frequency of input/output verification shall be based on the complexity and reliability of the computer or related system. A backup file of data entered into the computer or related system shall be maintained except where certain data such as calculations performed in connection with laboratory analysis, are eliminated by computerization or other automated processes. In such instances a written record of the program shall be maintained along with appropriate validation data. Hard copy or alternative systems, such as duplicates, tapes, or microfilm, designed to assure that backup data are exact and complete and that it is secure from alteration, inadvertent erasures, or loss shall be maintained.

Automatic and related equipment and controls are permitted in the regulations. The applications are quite diverse and can range from the reproduction of batch records, through the calculation of analytical data, to the control of operational processes and services. In production these controls can significantly improve the consistent performance of an operation, by removing the variability due to operator involvement. For example, a 10-minute blending step is likely to vary by several seconds routinely and significantly more if the operator is interrupted for some reason. Process validation studies should have demonstrated that such variability has no impact on product quality. However, these variabilities may impact on output and full process optimization may not be initiated until the prior step has been properly completed. A further benefit of automated control is that some operations may be performed over the entire 24-hour period with minimal human involvement; this has been of particular application to analytical procedures.

Industry had questioned the need to routinely check the accuracy of input/output data when using the validated computer system. The FDA modified the regulation, effective February 21, 1995, by adding the third sentence to §211.68(b). This adds very little clarification to the regulation. The preamble does state, “while increasingly sophisticated system safeguards and computerized monitoring of essential equipment and programs help protect data, no automated system exists that can completely substitute for human oversight and supervision.” Manufacturers are allowed to exercise their own judgment with respect to the extent and frequency of these checks, and industry/FDA disagreement is likely to continue.

Computerized systems have two main components, the system or process being controlled and the control system itself (computer hardware and software); both must be validated.

COMPUTER SYSTEMS VALIDATION

The CGMP regulations contain several references to validation (§211.68, §211.84, §211.110, and §211.133). Initial emphasis related primarily to sterile processing, and it was not until 1983, with the publication of the FDA “Guide to Inspection of Computerized Systems in Drug Processing,” that significant attention was focused on computer system validation.

In order to approach the subject in a coherent manner, some companies have established computer systems validation committees. This may include a steering committee with overview responsibility for policy and approval of protocols plus local facility committees to identify the systems requiring validation, draft protocols, and monitor progress.

There are four stages involved in computer system validation. These are design and specification (development), installation (qualification), operation (validation), ongoing operation (revalidation). These four stages have been integrated into the “life cycle approach” (Figure 1), which starts with the identification of user requirements, continues through the stages of development, installation, validation, operation, and maintenance, and ends only when the use of the system is discontinued.

The development stage involves several key steps:

1. The user must define what the computer system is expected to do. Other impacting factors should also be identified—environmental conditions in which the equipment will operate (temperature, humidity, electronic noise), backup procedures, report formats, and system security.
2. Documentation of the various steps and activities during development.
3. Testing of computer hardware including peripherals (terminals, printers, disk drives, etc.), controls and wiring before delivery.
4. Provision of as-built drawings.
5. Confirmation that software has been properly developed to meet user requirements, FDA Compliance Policy Guide 7132 a.15 includes three key points.
 - User firms should review the source code and supporting documentation for application-specific software. The user should also approve the software before implementation.
 - User firms should maintain the source code.
 - Dead code should be removed.

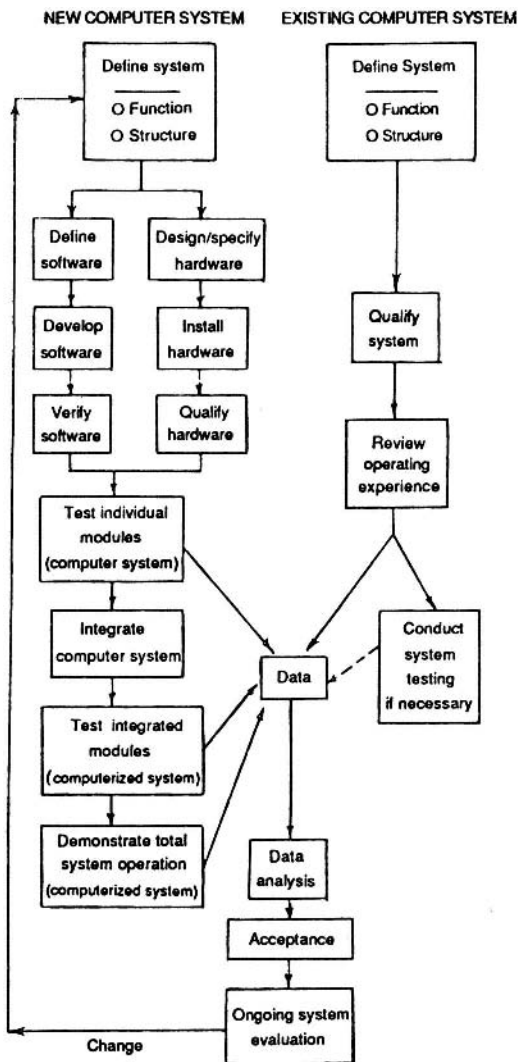


Figure 1 The validation life cycle approach. (Reprinted from Ref. 17.)

This guide, and its interpretation, resulted in significant discussion between vendors, users and the FDA. Vendors were particularly concerned about the proprietary nature of some source codes while the users were concerned about the impracticability of line-by-line review of source codes. It would appear that the situation can be resolved.

1. Vendor to provide written assurance that all software was developed by qualified personnel following defined procedures and maintaining full records of the developmental activities.
2. System documentation is made available to the user in readily understandable form.
3. Source code will be provided for application-specific software.

The installation evaluation initially applies only to hardware and is to confirm that the equipment, as installed, complies with the agreed development criteria. This stage could involve:

1. Confirm the wiring to the peripherals complies with drawings.
2. Conduct diagnostic checks.
3. Verify operation under the limits of the defined environmental conditions.
4. Verify signal levels and electrical noise.

After confirming the adequacy of hardware installation it is necessary to verify performance of the units of the computer system. This could include checking:

1. The polarity and range of each signal
2. The performance of sensors and control elements
3. The feedback data on equipment status
4. The software performance

The validation stage should not only confirm that the system operates within the defined criteria; it should also examine security and change procedures. System validation will usually be performed using an agreed protocol, which will define:

1. The number of operating runs required
2. The operational limits or ranges to be evaluated
3. The acceptance criteria
4. Who is to review and approve the data
5. Where the data are to be filed for permanent storage

The security of the system needs to be protected against unauthorized access, especially any which might result in unauthorized change to the system,

and also needs protection from damage due to environmental factors, including loss of power.

Where changes to software are necessary, these should be made only by designated qualified individuals, following approved procedures, and the changes must be fully documented.

Revalidation should ideally only need to be considered when there have been approved changes to the system. However, it may still be prudent to perform some revalidation at intervals to confirm that no unauthorized changes have been introduced or that cumulative minor changes have not modified the process.

§211.72 FILTERS

Filters for liquid filtration used in the manufacture, processing, or packing of injectable drug products intended for human use shall not release fibers into such products. Fiber-releasing filters may not be used in the manufacture, processing, or packing of these injectable drug products unless it is not possible to manufacture such drug products without the use of such filters. If use of a fiber-releasing filter is necessary, an additional non-fiber-releasing filter of 0.22 micron maximum mean porosity (0.45 micron if the manufacturing conditions so dictate) shall subsequently be used to reduce the content of particles in the injectable drug product. Use of an asbestos-containing filter, with or without subsequent use of a specific non-fiber-releasing filter, is permissible only upon submission of proof to the appropriate bureau of the Food and Drug administration that use of a non-fiber-releasing filter will, or is likely to, compromise the safety or effectiveness of the injectable drug product.

This subsection is essentially out of place here since it has restricted applicability to the manufacture of injectable products for humans. The later introduction of limits on particulate matter in injectables encouraged the move away from fiber-releasing filters. The ban on use of asbestos filters, without FDA approval, relates not only to reduction in particulate matter in injections but also to minimization or elimination of worker exposure to airborne asbestos fibers.

Although asbestos-based sterilizing filters have not been used for many years, the German Federal Health Office (Bundesgesundheitsamt) did find low levels of asbestos particles in some injections and in 1993 imposed limits. The limits proposed were no fibers with a length exceeding 2.5 μm and a tentative limit of not more than 10,000/unit dose with a length between 1 μm and 2.5 μm . Industry considered these requirements to be unnecessary and impractical. There is only one detection method currently able to quantitate asbestos at these levels—the transmission electron microscope, which is not universally available,

and there is no standardized procedure for the method. To date, other countries have not followed Germany.

More important for sterilizing filters are extractables and validation of filtration effectiveness. Many companies, with the support of the filter manufacturers, have used a matrix approach to address these issues, provided there is a scientific justification.

EXAMPLES OF OBSERVATIONS FROM FDA 483 CITATIONS

1. Worst-case conditions are not undertaken during the validation study.
2. Cleaning failures noted in the ongoing cleaning validation program are not investigated and corrected.
3. The maintenance support group was using an obsolete SOP for maintenance and calibration of equipment.
4. The firm's cleaning validation program has not addressed how long a product can remain in the processing equipment before the equipment must be cleaned.
5. There are no maintenance records for the tableting machines to indicate when routine repair and replacement of parts is performed.
6. Filters used to sterilize bulk drug solutions are not being subjected to a prefiltration integrity test.
7. There are no written procedures for calibration and preventive maintenance of laboratory instrumentation.
8. The record generated during the calibration of the fluid bed dryer sensors and chart recorder appear inadequate in that there is no written protocol for this operation; the probes of the original Digistrip recorder used to calibrate the Digistrip thermocouples had not been calibrated since. . . .
9. There are no qualification studies performed on equipment to assure that they perform as intended.

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Following study of this chapter, it might be helpful for staff review, to discuss specific guides provided by the FDA to their field staff and others, that are pertinent as Regulatory Action Guidance.

Sec. 425.400 Computerized Drug Processing; Input/Output Checking (CPG 7132a.07)

BACKGROUND:

Section 211.68 (automatic, mechanical, and electronic equipment) of the Current Good Manufacturing Practice Regulations requires, in part, that input to and output from the computer or related system of formulas or other records or data be checked for accuracy. This requirement has generated questions as to the need for and extent of checking a computer's input and output.

The agency received several petitions to delete or modify the requirement on the grounds that a validated computer system need not have its input/output routinely checked. The request to delete or modify the requirement was denied because our experience has shown that input/output error can occur, even in validated systems. Printouts, for example, can contain errors as a result of faulty input, programming, or equipment malfunction. More significantly, there is the human element which can induce errors. At worst, input/output errors can result in serious production errors and distribution of adulterated or misbranded products. Several recalls have, in fact, been conducted because of insufficient input/output checks.

Despite the general need for input/output checks, not all input and output need be checked. The regulation is, in fact, deliberately silent on the required frequency and extent of data checking to afford firms the necessary flexibility. Also, the use of efficient input edits, for example, could mitigate the need for more detailed manual data checks.

POLICY:

Input/output checks of data for computer systems, as required by 21 CFR 211.68, are necessary to assure the quality of a drug product processed using such systems. The extent and frequency of input/output checking will be assessed on an individual basis, and should be determined based upon the complexity of the computer system and built in controls.

Issued: 9/20/82

Reissued: 9/4/87

Sec. 425.500 Computerized Drug Processing; Identification of “Persons” on Batch Production and Control Records (CPG 7132a.08)

Section 211.188(b)(11) of the Current Good Manufacturing Practice Regulations requires that batch production and control records include documentation that each significant step in the manufacture, processing, packing, or holding of a batch was accomplished, including identification of the persons performing, directly supervising or checking each significant step in the operation.

Questions have been raised as to acceptable ways of complying with this requirement when the “person” performing, supervising or checking each step is, in fact, not a human being, but rather an automated piece of equipment, such as a computer system.

The intent of the regulation is to assure that each significant step in a process was, in fact, performed properly and that there is some record to show this. It is quite possible that a computerized system can achieve the same or higher degree of assurance. In this case it may not be necessary to specifically record the checks made on each of a series of steps in the production of the product.

When the significant steps in the manufacturing, processing, packing or holding of a batch are performed, supervised or checked by a computerized system an acceptable means of complying with the identification requirements of 21 CFR 211.188(b)(11) would consist of conformance to all of the following:

1. Documentation that the computer program controlling step execution contains adequate checks, and documentation of the performance of the program itself.
2. Validation of the performance of the computer program controlling the execution of the steps.
3. Recording specific checks in batch production and control records of the initial step, any branching steps and the final step.

NOTE: In assessing how well a computer system checks a process step it is necessary to demonstrate that the computer system examines the same conditions that a human being would look for, and that the degree of accuracy in the examination is at least equivalent.

Issued: 11/2/82
Reissued: 9/4/87

6

Control of Components and Drug Product Containers and Closures (Subpart E)

§211.80 GENERAL REQUIREMENTS

- (a) There shall be written procedures describing in sufficient detail the receipt, identification, storage, handling, sampling, testing and approval or rejection of components and drug product containers and closures; such written procedures shall be followed.
- (b) Components and drug product containers and closures shall at all times be handled and stored in a manner to prevent contamination.
- (c) Bagged or boxed components of drug product containers, or closures shall be stored off the floor and suitably spaced to permit cleaning and inspection.
- (d) Each container or grouping of containers for components or drug product containers, or closures shall be identified with a distinctive code for each lot in each shipment received. This code shall be used in recording the disposition of each lot. Each lot shall be appropriately identified as to its status (i.e., quarantined, approved, or rejected).

The general requirements again emphasize the need for written procedures which are to be followed. Some detail on procedures and compliance is presented later under Section 211.100.

During storage, handling, and sampling, materials are potentially vulnerable to contamination. Warehouses are designed to allow easy access for delivery

vehicles; however, this also allows access to rodents, insects, birds, extraneous dust, and vehicle exhaust fumes.

This unwanted access can be minimized by separating the actual delivery area from the main storage area by doors or air curtains. Certain raw materials, such as sugar and starch, can also attract creatures and it is important that any spillages be quickly cleaned up. Storage on pallets or racks facilitates cleaning. These important precautions still are unlikely to completely prevent access to insects and other sources of contamination. Consequently, extermination or elimination programs are also required. Rodents usually can be controlled by the placement of baitless traps; the use of poison bait is not acceptable in a pharmaceutical establishment. Insects are frequently eliminated by the use of electric exterminators, while birds may be trapped and then removed from the premises.

When containers of materials are opened for sampling the contents have an increased vulnerability for contamination from other materials, microorganisms, or foreign particulate matter (dust). Warehouse conditions may not be suitable for sampling and a separate area may be required (see §211.84). This may consist of a separate room provided with improved air handling systems, readily cleanable surfaces and availability of dust extraction hoods (i.e., similar to a dispensing operation). Alternatively, laminar flow cabinets may be used with their own self-contained air and dust handling systems. These can be designed to be moveable and can be taken to the material to be sampled; this may be of more value for resampling of materials that have already been moved into storage than for newly received deliveries.

The requirement for a distinctive code for each lot of components received can be met by retaining the supplier coding where this is adequate. However, most companies prefer to use their own coding system rather than try to work with the various systems used by different suppliers. This requires that the distinctive number be physically applied to some or all of the containers. The intention is to maintain batch identity of the components throughout the production operation and consequently the number of containers requiring labeling will depend on the predicted usage of the components. For example, if components are used in complete pallet loads, it should be acceptable to label only one container per pallet. Should this approach be used, then it must be clearly demonstrated that the procedure is effective in maintaining batch identity and usually requires that the labeled container is the last one to be removed from storage. It is now becoming common for manufacturers to apply bar codes to materials, which can be used to effectively monitor the use and movement of the material through its life cycle.

The regulation also requires status identification. This has, on occasion, been interpreted as physical labeling of containers. However, since the physical separation of materials can be replaced by an appropriate system [Section 211.42(c)], it would seem reasonable that the same approach can be used with respect to status identification.

§211.82 RECEIPT AND STORAGE OF UNTESTED COMPONENTS, DRUG PRODUCT CONTAINERS, AND CLOSURES

- (a) Upon receipt and before acceptance, each container or grouping of containers of components, drug product containers, and closures shall be examined visually for appropriate labeling as to contents, container damage or broken seals, and contamination.
- (b) Components, drug product containers, and closures shall be stored under quarantine until they have been tested or examined, as appropriate, and released. Storage within the area shall conform to the requirements of Section 211.80.

Visual examination of materials on receipt is an important quality step. This should confirm that the correct material has been delivered, and if any physical damage has occurred its potential impact on quality needs to be considered. Broken seals on containers may indicate that the container has been opened somewhere during transit, and the material may have been exposed to unacceptable environmental conditions. The possibility of deliberate sabotage is very real as well, and suppliers should be encouraged to use seals with unique designs or logos to minimize this potential for deliberate tampering. Since seals on outer containers are sometimes broken or lost inadvertently during transportation, examination of any inner seals may be required before a final decision can be made. Containers should also be examined for physical deformation and for visible signs of spillage from other materials as well as for potential rodent attack. These situations will require additional evaluation and could result in rejections. Users of components during the production process should also be required to conduct visual inspection prior to use. This additional check is particularly important if each container has not been individually inspected or opened earlier. In fact, low-frequency defects in packaging components are more often detected during the filling/packaging process than by sampling on receipt.

It is also essential to confirm the name of the supplier; this is elaborated upon in §211.84. When materials are purchased through agents, these should be requested to identify the actual producer; otherwise the agent may interchange producers according to availability and price and without notification. Since quality cannot be assured solely on the basis of testing, any change in supplier may have an impact on product quality. To eliminate any potential impact it may be necessary to perform additional testing other than that included in the specification. Accelerated stability studies comparing the current and new material are required and also, on occasion, accelerated comparative stability on the dosage form itself. Obviously this could not be done if the customer was unaware of the change in supplier.

Section (b) refers to storage under quarantine until release. The acceptability of a system as an alternative to physical separation has been indicated previously in §211.42(c).

§211.84 TESTING AND APPROVAL OR REJECTION OF COMPONENTS, DRUG PRODUCT CONTAINERS, AND CLOSURES

(a) Each lot of components, drug product containers, and closures shall be withheld from use until the lot has been sampled, tested, or examined, as appropriate, and released for use by the quality control unit.

The need to withhold materials for use until released by quality control is laudable and equates to the normal situation. However, there are occasions when for a variety of reasons materials arrive at a plant site and are required for immediate use. The reason for this could include late delivery, rejection of the scheduled delivery, unexpected increase in sales, or rejection of the scheduled batch of drug product. These situations could be exacerbated by lengthy component testing such as microbial evaluation. There would seem to be no reason why the drug product manufacturer cannot use the material while it is undergoing testing and accept the possible risk of a product rejection. Obviously the manufacturer would be cognizant of these potential financial risks and before initiating such an action would evaluate material and product history and the magnitude of the added value. However, the FDA have specifically stated that such an approach is not acceptable since this “increases the risk to the consumer that an unsatisfactory lot might erroneously be released.” There is little or no foundation for this opinion.

Deliveries of material to bulk storage requires special mention. It is frequently impractical to hold a delivery vehicle until material can be fully evaluated. In such cases it is usual to ensure that the certificate of analysis accompanies the delivery and that the more sensitive tests are performed before the material is discharged into the bulk storage system. In the event that the full analysis identifies a problem it may be necessary to quarantine the contents of the storage tank until a comprehensive evaluation has been performed.

When a second delivery of a previously released material is received, it is still necessary to sample and evaluate. The conditions to which the later delivery may have been exposed could have differed from the original delivery. The same level of evaluation may not be necessary but any parameter that might be affected by shipping and storage conditions should be examined.

(b) Representative samples of each shipment of each lot shall be collected for testing or examination. The number of containers to be sampled, and the amount of material to be taken from each container, shall be based upon

appropriate criteria such as statistical criteria for component variability, confidence levels and degree of precision desired, the past quality history of the supplier, and the quantity needed for analysis and reserve where required by §211.70.

One would hope that quality variability would rarely be a reason for increasing sample size. However, for new suppliers it may be necessary to apply more extensive sampling and evaluation until consistency is demonstrated. This could also be the case for a new dosage form, which, although validated using a minimum of three batches, could still undergo process improvement/optimization. Additional amounts of sample could allow more extensive evaluation of the material in relation to these optimization studies.

(c) Samples shall be collected in accordance with the following procedures:

(1) The containers of components selected shall be cleaned where necessary, by appropriate means.

(2) The containers shall be opened, sampled, and resealed in a manner designed to prevent contamination of their contents and contamination of other components, drug product containers, or closures.

(3) Sterile equipment and aseptic sampling techniques shall be used when necessary.

(4) If it is necessary to sample a component from the top, middle and bottom of its container, such sample subdivisions shall not be composited for testing.

(5) Sample containers shall be identified so that the following information can be determined: name of the material sampled, the lot number, the container from which the sample was taken, the date on which the sample was taken, and the name of the person who collected the sample.

(6) Containers from which samples have been taken shall be marked to show that samples have been removed from them.

The process of sampling can itself pose risks of contamination. For this reason containers may need to be cleaned—a vacuum system is very effective. Generally an air-blowing system should be avoided because this is more likely to spread a potential problem. Containers should be opened for sampling in an acceptable environment that will not expose the material to further risk. For drug substances and excipients it is preferable to provide a sampling area with environmental conditions similar to those in manufacturing. This sampling area may be a designated room, but a useful alternative is a portable laminar flow hood with dust extraction capability that can be placed over the materials to be sampled. This negates the need to move materials from quarantine to another area for sampling and then returning to quarantine afterward. Containers and closures can usually be sampled in the warehouse, but any outer protective coverings should be securely replaced.

Materials requiring microbiological evaluation need to be sampled under more rigorous conditions involving the use of sterile equipment. Employees must be properly trained in such sampling techniques.

The regulations do not preclude the composing of samples for testing except as indicated in (c)(4). This would seem to be an unnecessary detail. If there is some doubt about the homogeneity of a component, it may be advisable to evaluate this by taking samples from various positions in the container. Obviously the compositing of these samples would be scientifically invalid.

(d) Samples shall be examined and tested as follows:

(1) At least one test shall be conducted to verify the identity of each component of a drug product. Specific identity tests, if they exist, shall be used.

(2) Each component shall be tested for conformity with all appropriate written specifications for purity, strength, and quality. In lieu of such testing by the manufacturer, a report of analysis may be accepted from the supplier of a component, provided that at least one specific identity test is conducted on such component by the manufacturer, and provided that the manufacturer establishes the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals.

(3) Containers and closures shall be tested for conformance with all appropriate written procedures. In lieu of such testing by the manufacturer, a certificate of testing may be accepted from the supplier, provided that at least a visual identification is conducted on such containers/closures by the manufacturer and provided that the manufacturer establishes the reliability of the supplier's test results through appropriate validation of the supplier's test results at appropriate intervals.

(4) When appropriate, components shall be microscopically examined.

(5) Each lot of a component, drug product container, or closure that is liable to contamination with filth, insect infestation, or other extraneous adulterant shall be examined against established specifications for such contamination.

(6) Each lot of a component, drug product container, or closure that is liable to microbiological contamination that is objectionable in view of its intended use shall be subjected to microbiological tests before use.

Components, containers, and closures used for production of pharmaceuticals must obviously comply with their quality specifications. As suppliers introduce effective procedures, and embrace the principles of vendor certification, the need for customer testing is reduced. However, basic caution and the CGMP regulations do require that some testing is performed. For a new, or a not too reliable, supplier, it will usually be necessary for the customer to perform full testing. Suppliers should be encouraged to provide certificates of analysis which can be used to compare supplier and customer results; this is part of the process of validating a supplier, leading to either vendor approval or vendor certification

status. The vendor approval status indicates that the supplier has a good record, but probably still relies to some extent on selecting out defectives rather than preventing their occurrence. When certificates of analysis are provided they should refer to all of the agreed tests in the specification. Actual values should be given for quantitative tests. The words “passes test” or “conforms” are not an analytical report, but judgments, which have no place on a certificate of analysis; they make it impossible to compare customer and supplier results and can hide results which show a trend over consecutive deliveries or which are close to specification limits. This does not apply to limit tests which are specifically designed to indicate whether the material is better or worse than the limit standard. The certificate of analysis must be signed and dated by a competent person from the supplier. Any significant differences in results between supplier and customer must be investigated and the cause identified and corrected. The customer must also check the values of a certificate of analysis to confirm that they do actually comply with the specification.

Once supplier confidence has been established (approval or certification), it may be possible for the customer to move to a reduced level of testing. The regulations still insist on a minimum of one identity test which for containers and closures may be visual. For chemical components the identity test should if possible be specific, and infrared spectra or chromatographic procedures are increasingly used for this purpose. Any parameters that could be subject to change during shipping and that could have a significant impact on quality need to be included in the reduced testing protocol. These protocols must clearly define the conditions to be met before reduced testing can be introduced, indicate that the procedure is material *and* supplier related, the frequency of full testing, and the circumstances that require a return to full testing. It must be emphasized that the customer QC department is responsible for the release of purchased materials into production, and consequently reduced testing should only be introduced when there is proven confidence in the supplier.

VENDOR CERTIFICATION

In recent years emphasis has been on the application of validation techniques to increase the level of quality assurance. This has extended to suppliers and is most usually referred to as vendor certification. Vendor certification is a system that assures that a supplier's product is produced under controlled conditions, resulting in consistent quality conformance. Being based on the principle of defect prevention, rather than defect detection and inspection, it significantly reduces the need for customer inspection.

Vendor certification is a supplier–customer partnership and can only be successful with the full involvement and agreement of both partners. Several key steps are involved in the certification process.

Customer Teams

Several functions need to be involved in establishing a vendor certification process. Typically the team will include representatives from manufacturing, package engineering, purchasing and quality assurance with support, as appropriate, from other disciplines such as finance and research and development. The initial task of the team will be to define the objectives and potential benefits and to write a process that can be used as a basis for discussion with suppliers.

Supplier Selections

The long-term intent would be to certify all suppliers but this is likely to take considerable time and effort. The initial selection of potential partners should take into account the supplier's history in terms of quality, delivery, and support service as well as the importance of the specific material to the business. Vendor certification has a higher chance of success with a supplier who already has a high commitment to quality and customer service. Also, when one successful certification has been implemented and benefits can be perceived, the program will gain added emphasis.

Initial Supplier Contacts

The proposed process will be discussed with the supplier. After agreement on the concept, which must include senior management, the individual components of the process can be reviewed and adapted for mutual satisfaction.

Process Elements

- a. Supplier process. Some or all of the customer vendor certification team should visit the supplier's plant to gain an understanding of the production process and the key elements which impact on the achievement of quality standards. Where a material may be supplied from more than one plant of the supplier, each plant must be treated as a separate entity for certification purposes.
- b. Specifications. A detailed review should be made of product specifications with particular reference to legal requirements (compendia, FDA, etc.) and fitness for use. This latter point is likely to require a supplier understanding of the customer's process; in this way it may be possible to relax certain less critical specification parameters while tightening or increasing the level of assurance on more critical parameters. This can be particularly important with packaging components where improvements in some areas can dramatically impact on line speeds and effi-

ciency and with particle size of powder ingredients. Obviously test methods should, where possible, be identical. Where this is not possible, equivalence must be demonstrated.

- c. Process evaluation. The supplier must have suitable equipment to monitor the process. This equipment must be routinely calibrated and test methods validated. Statistical process control techniques will usually be applied to demonstrate that the process remained under control, within acceptable operating ranges, throughout each production run. The ability to understand control data and to use it for evaluating process variability must be demonstrated; the “blind” application of statistical process control charts is not sufficient. Process control data for several batches, chosen at random, should be reviewed to confirm supplier compliance. It must be emphasized that vendor certification requires assurance that the supplier’s process is under control and that the required quality standards are not being achieved by inspecting out substandard material. Increasingly, vendors are being requested to demonstrate that their production processes are validated, especially for the manufacture of bulk pharmaceutical chemicals. To demonstrate commitment to quality for other components, some vendors have opted for ISO 9000 certification. As indicated in [Chapter 21](#), this certification does not necessarily assure consistent quality.

Process and Specification Changes

Another important element in the vendor certification process is the procedure for handling any changes to the process or the specification. Any proposed changes must be clearly documented, with reasons and supporting data, and be reviewed and accepted by the customer prior to introduction. Some changes may require customer evaluation and even FDA approval before acceptance.

A similar procedure should be in place in the event the customer intends to change the specification. Any proposed changes to the customer’s process which could impact on the usability or performance of the supplier’s material also require prior review and agreement with the supplier. For example, if the customer was contemplating replacement of a packaging line, there would need to be discussions with the supplier of the packaging components. Having established a working partnership that can manage change, it should be possible to work together to identify areas for improvement.

Customer Inspection

After it has been confirmed that a supplier has a controlled process, there usually will be a period when both parties evaluate material quality and compare data.

This provides the needed assurance that supplier and customer have comparable evaluation ability and minimizes future potential for disagreements that are due to test results rather than atypical product. The customer may also wish to revert to comprehensive evaluation at intervals as an additional assurance. Vendor certification provides a strong basis for the application of reduced testing by the customer. If the supplier's process is under control, any evaluation by the customer should only have value with respect to any changes during shipment. Sections 211.84(a) and (d) do allow for reduced testing, but the elimination of incoming material testing by the customer is precluded currently by 211.84(d)(2) and (3). The customer should perform audits of the supplier's process at appropriate intervals. This can be a useful opportunity to review the entire vendor certification process and to evaluate success.

Supplier Reporting

Since vendor certification is a partnership, it is important that both supplier and customer are kept informed of each other's difficulties. The supplier must notify the customer of any atypical situations or process deviations prior to shipping material so that any additional testing or evaluations may be performed. The supplier should also provide certificates of compliance or certificates of analysis for every batch—formatted in a manner which is acceptable to the customer. The customer should also provide feedback to the supplier with respect to compliance with specification, performance in use, and delivery service.

Decertification

Certification results in a high level of reliance on the supplier: reduced incoming inspection, reduced inventories, higher output. Any failure by the supplier can therefore have serious consequences and may require decertification of that supplier for that material. Depending on the nature of the problem it may be possible to work with the supplier to reestablish certification, or the supplier may be relegated to a lesser status such as "approved" or "preferred." The main result of vendor certification is an assured reduction in quality variability which provides several benefits.

- a. The tighter specification ranges usually result in higher yields and reduced equipment downtimes for the supplier, thereby providing an opportunity to reduce prices or minimize price increases. A similar situation can occur with the customer and should also result in more consistent product quality.
- b. More consistently compliant batches can result in lower inventories for both supplier and customer. This reduces the cost of carrying inventory.

It also reduces the level of write-off associated with materials that have become unusable because of extended storage or obsolete because of policy changes.

- c. Reduced testing by the customer eliminates some testing costs but more importantly can make materials available to production more quickly. This allows further inventory reductions and is also of benefit when materials are urgently required for unexpected production.

(e) Any lot of components, drug product containers, or closures that meets the appropriate written specifications of identity, strength, quality, and purity and related tests under paragraph (d) of this section may be approved and released for use. Any lot of such material that does not meet such specifications shall be rejected.

Any lot of components, containers, or closures not meeting the specification is to be rejected. This does not preclude recovery by an appropriate rework or inspection procedure provided the material after this rework meets the specification. However, this could become a problem if specifications are set without full regard to their impact on product quality. For example, if color standards for cartons are set as specifications, this could prevent the use of slightly atypical material in an urgent situation—even though the quality impact may be negligible. In such instances it may be advisable to include certain noncritical parameters as action levels, provided the procedures clearly define who makes the decision. There is an obvious need for supplier and customer to agree on specifications; without such an agreement, there could be some pressure to use atypical components simply to avoid financial loss.

§211.86 USE OF APPROVED COMPONENTS, DRUG PRODUCT CONTAINERS, AND CLOSURES

Components, drug product containers, and closures approved for use shall be rotated so that the oldest approved stock is used first. Deviation from this requirement is permitted if such deviation is temporary and appropriate.

Using oldest stock first helps to reduce the possibility of contamination and to assure that material conforms to appropriate requirements. Since it may be desirable to package using a single lot of components, containers, or closures, an exemption from strict use of oldest stock first is provided. Other legitimate uses of the exemption are for evaluation of a new supplier, or new equipment or processes with respect to a preferred lot of materials, or the temporary physical inaccessibility of the oldest stock.

Materials management systems now include a need to reevaluate material after a predetermined time and prior to use. This will further minimize the chance that materials in an unsuitable condition will be used (see also §211.87).

§211.87 RETESTING OF APPROVED COMPONENTS, DRUG PRODUCT CONTAINERS, AND CLOSURES

Components, drug product containers, and closures shall be retested or re-examined, as appropriate, for identity, strength, quality, and purity and approved or rejected by the quality control unit in accordance with §211.84 as necessary, e.g., after storage for long periods or after exposure to air, heat or other conditions that might adversely affect the component, drug product container, or closure.

The release of components, containers, and closures for use cannot be for an indefinite time. During storage, degradation may occur, moisture may be absorbed, or materials may simply become covered in dust. Reevaluation time-scales are usually developed from historical data. Except for particularly sensitive materials, it is usual to settle for one time period—often one year. Either the product release label or the system should clearly indicate when materials are to be reevaluated. This reevaluation will not usually require full testing but only examination of those parameters known to be subject to change. For infrequently used materials, reevaluation may be delayed until the material is required.

Under normal circumstances materials will be used before they become eligible for reevaluation. Consequently, when reevaluation is necessary the reason for the material still being around should be investigated. The usual reasons include minimum purchase quantities and changes in forecast, but occasionally this can identify a flaw in the purchasing or planning processes. A further point to be considered when using older materials is the impact on the stability of the dosage form. Degradation is not always linear, and in some instances a limited accelerated stability study may prove advisable.

An important factor in reevaluation is the comprehensiveness of the material specification. For some materials the specifications may have been derived many years ago and the evaluation of ingredients may not meet current expectations. This applies to some of the older bulk drugs in the USP. In these cases it may be necessary to supplement the existing specification with additional degradation and impurity evaluations. Also, when reevaluating materials the extent of changes should be considered even for parameters still within specifications.

For sensitive materials, care should be taken to store them under the appropriate conditions where these are specified. Where not specified it may still be

advisable to identify and use positions in the warehouse that are least susceptible to adverse climatic changes.

§211.89 REJECTED COMPONENTS, DRUG PRODUCT CONTAINERS, AND CLOSURES

Rejected components, drug product containers, and closures shall be identified and controlled under a quarantine system designed to prevent their use in manufacturing or processing operations for which they are unsuitable.

This section reaffirms what was reviewed earlier in Section 211.42(c)(2). Although a segregated reject area is not required if an adequate control system exists, many companies do segregate reject materials. This is an added precaution against inadvertent use.

FDA investigators frequently use a visit to the reject area as a potential source of deficiencies. If rejections occur it is possible to assume that the vendor process is not adequately under control, and an evaluation of the cause should have been performed and documented.

§211.94 DRUG PRODUCT CONTAINERS AND CLOSURES

- (a) Drug product containers and closures shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug beyond the official or established requirements.
- (b) Container closure systems shall provide adequate protection against foreseeable external factors in storage and use that can cause deterioration or contamination of the drug product.
- (c) Drug product containers and closures shall be clean and, where indicated by the nature of the drug, sterilized and processed to remove pyrogenic properties to assure that they are suitable for their intended use.
- (d) Standards or specifications, methods of testing, and, where indicated, methods of cleaning, sterilizing, and processing to remove pyrogenic properties shall be written and followed for drug product containers and closures.

The assessment of suitability of containers and closures is described in Section 211.166 (stability testing). The United States Pharmacopeia, <661>, provides information on specifications and test methodology for a range of container materials. These include:

1. Light transmission for glass and plastics
2. Chemical resistance for glass
3. Arsenic extraction from Type 1 glass

4. Biological tests on plastics used for parenterals
5. Physicochemical tests on plastics used for parenterals
6. Biological tests on plastics used for ophthalmic products
7. Chemical tests on polyethylene containers for dry oral dosage forms

These tests may also be modified to apply to the use of plastics other than polyethylene and the use of plastics with liquid dosage forms. The USP is currently drafting a monograph on polyethylene terephthalate (PET). Where other plastics are involved, any specific signal compounds may need evaluation, e.g., vinyl chloride monomer levels from polyvinylchloride (PVC) containers.

A separate section of the USP, <381>, addresses elastomeric closures for injections. The monograph provides details of both biological and physicochemical tests on extracts from elastomeric closures. The monograph also requires the customer to review all the ingredients of the closure formulation to assure that no known or suspected carcinogens or other toxic substances are included. Since many elastomeric formulations are considered proprietary by the manufacturer such a review may not always be possible. However, the manufacturer should be asked to confirm the absence of carcinogenic and toxic additives. The potential impact of storage, cleaning procedures, and product on the suitability for use are also to be evaluated but no test methodology is provided.

A container closure system usually serves several roles: to prevent egress (leakage) of the contents, especially for liquids; to prevent ingress of microorganisms, especially for sterile products; to provide access by the consumer to the contents. The evaluation of container closure performance during storage and transportation will be addressed in the section on stability (§211.166). Consumer acceptability, with the exception of child-resistant closures for which there are defined test methods and acceptance criteria, is often given minimal attention. The United States requires that over-the-counter (OTC) medicines be packaged with at least one tamper-resistant (tamper-evident) feature. Such features may be part of a container closure system, as in the case of seals over the mouth of a bottle, and require stability evaluation. Others, such as neck seals and carton overwraps, do not impact on stability. The initial CGMP regulations did not address product tampering specifically, but the wording in (b), “protection against foreseeable external factors in storage and use,” could be considered to apply. Tampering, although rare, has become a “foreseeable” possibility since the death of seven people by the deliberate contamination of Tylenol® Capsules with cyanide in 1982 and resulted in the addition of §211.132.

In addition to confirming the suitability of containers and closures, there must also be available specifications defining composition and dimensions. The compositions of many plastic and elastomeric materials are considered confidential by suppliers. Consequently, close working relations should be established with such suppliers to ensure that they use only acceptable additives and that no

changes are made without prior notification with adequate time for evaluation and FDA approval where required.

EXAMPLES OF OBSERVATIONS FROM FDA 483 CITATIONS

1. Vendor audit reports listed significant observations. There were no vendor responses.
2. Sampling of containers/closures is not based on appropriate statistical criteria.
3. The firm has not included a pyrogen and/or bacterial endotoxin specification for active drug substance raw material.
4. Several batches of tablets were rejected because the active raw material did not meet the firm's established bulk density specifications. No explanation was given in the process validation report as to how bulk density affects the finished product.
5. The firm is aware that . . . has shown marked degradation over time but no testing was performed on current lots in order to justify the one-year material storage time limitation.

SUGGESTED READINGS

1. K. G. Beagley, Should You Certify your Vendors? *Pharm. Med. Pack. News*, Sept., 34, 1994.
2. PDA Supplier Certification Task Force, Supplier Certification—A Model Program, *J. Parent. Sci. Technol.*, 43(4), 151, 1989.
3. PMA, Guidelines for Vendor Certification, 1989.

Recommended: See sample agreement as to indemnity and guarantee.

SAMPLE AGREEMENT: EXCHANGE OF CONFIDENTIAL INFORMATION BETWEEN VENDORS AND VENDEES; PRIME AND COMPONENT MANUFACTURERS

CONFIDENTIALITY AGREEMENT

This Confidentiality Agreement, dated as of _____ is between Sterling Drug Inc., hereinafter "Sterling", with offices at 90 Park Avenue, New York, NY 10016, and _____, for himself and in representation of _____, addresses following: _____, hereinafter called "Recipient", who will be granted access by Sterling to certain information reposing in litigation files as requested by _____.

1. Information means names, titles of all persons, natural or artificial within such litigation files, all other information, details, data, communicated within same, provided for access to Recipient together with all portions of research, process, analyses, studies and other documents prepared by or for the benefit of being in its notice or defense. For their purposes of review as to liability and in consideration of being provided with access to the Information, Recipient agrees to treat the Information within the terms of this Agreement.

2. Recipient will keep all Information confidential. Without the prior written consent of Sterling, Recipient will not disclose any information to any third party, except to Recipient's employees who need to know such Information for purposes of the evaluation by Recipient of the aforesaid transaction, and will use the Information only for the purpose of such evaluation.

3. Recipient warrants that each of its employees to whom any Information is revealed shall previously have been informed of the confidential nature of the Information and have agreed to be bound by the terms and conditions of this Agreement applicable to Recipient. Recipient shall ensure that the Information is not used or disclosed by such employees except as permitted by this Agreement and shall be responsible for any breach of this Agreement.

4. All Information shall remain the property of Sterling, and if copies of such materials are made, with Sterling's permission, such copies will be treated similarly as Information hereunder.

5. The obligations of confidentiality and non-use set forth in this Agreement shall not apply to any portion of the Information which is disclosed by Recipient pursuant to a requirement of law, provided that Recipient has complied with the provisions set forth in paragraph 6.

6. If Recipient becomes legally required to disclose any Information, Recipient will give Sterling prompt notice of such fact so that Sterling may obtain a protective order or other appropriate remedy concerning any such disclosure and/or waive compliance with the non-disclosure provisions of this Agreement. Recipient will fully cooperate with Sterling in connection with Sterling's efforts to obtain any such order or other remedy. If any such order or other remedy does not fully preclude disclosure or Sterling waives such compliance, Recipient will make such disclosure only to the extent that such disclosure is legally required and will use its best efforts to have confidential treatment accorded to the disclosed Information.

7. Recipient acknowledges that Sterling makes no representation or warranty as to reliability, accuracy or completeness of any of the Information, except for any such representation or warranty that may be made in any definitive written agreement that may be executed and delivered after the date hereof by Recipient and Sterling with respect to the transaction referred to in paragraph 1. Recipient agrees that neither Sterling nor any of Sterling's agents, representatives or employees shall have any liability to Recipient arising from the Information or such transaction except as may arise out of any such definitive agreement.

8. Nothing herein shall be construed as giving Recipient any right, title, interest in or ownership of Information, and with respect to any portion thereof which is or becomes public information and is now or hereafter becomes covered by any patent, Recipient's rights with respect thereto shall be subject to all rights of the patent owner and/or licensee.

9. For the purposes of this Agreement, specific information disclosed as part of Information shall not be deemed to be in the public domain or in the prior possession of Recipient merely because it is embraced by more general information in the public domain or by more general information in the prior possession of Recipient.

10. This Agreement constitutes the entire agreement between Sterling and Recipient relating to the subject matter hereof and supersedes and replaces all prior writings, discussions and rights relating to the subject matter hereof. This Agreement may only be amended by a written instrument signed by both parties hereto. No obligation of any kind is assumed by or implied against either party hereto except for those obligations expressly stated herein.

11. This Agreement shall be governed by and construed in accordance with the laws of the State of New York applicable to contracts entered into and wholly to be performed within the State of New York.

12. Delay or failure to exercise any right or remedy hereunder shall not impair such right or remedy or be construed as a waiver thereof or as acquiescence in a breach of this Agreement. Any single or partial exercise of any right or remedy shall not preclude any other or further exercise thereof or the exercise of any other right or remedy.

13. This Agreement shall survive any termination of Recipient's evaluation of the transaction referred to in paragraph 1 and of discussions between Recipient and Sterling concerning such transaction, shall be binding upon Recipient and its successors for a period of five (5) years from the date hereof, and shall inure to the benefit of and shall be enforceable by Sterling, its successors and assigns.

14. Recipient hereby irrevocably consents to the jurisdiction of the courts of the State of New York and of any Federal court located in such State in connection with any action, suit or proceeding arising out of or relating to this Agreement, and waives personal service of any summons, complaint or other process and agrees that service thereof may be made by certified or registered mail directed to Recipient at its address given above in this Agreement.

STERLING DRUG INC.

By: _____
Name: _____
Title: _____

Recipient: _____

By: _____
Name: _____
Title: _____

7

Production and Process Controls (Subpart F)

§211.100 WRITTEN PROCEDURES; DEVIATIONS

- (a) There shall be written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess. Such procedures shall include all requirements in this subpart. These written procedures, including any changes, shall be drafted, reviewed, and approved by the appropriate organizational units and reviewed and approved by the quality control unit.
- (b) Written production and process control procedures shall be followed in the execution of the various production and process control functions and shall be documented at the time of performance. Any deviation from the written procedures shall be recorded and justified.

These two subsections embody the basic underlying concept of CGMP: there shall be adequate written procedures that have been approved by responsible persons, and for which there is documentation that the procedures have been followed.

The drafting and approval of important procedures such as these cannot be left to chance. Written standard operating procedures (SOPs) define how things are to be done and provide a basis for the training of new or relocated personnel. SOPs are a fundamental extension of the CGMPs—the latter ideally should define what is to be achieved, while the SOPs provide company specific approaches

on how to meet these requirements. There should be a master SOP, which describes the overall procedure—how to initiate/revise an SOP, format, who should review and approve (with defined areas of responsibility), frequency of routine review (often every two years), mechanism of issue and replacement of outdated versions, training. The apparently straightforward clerical activity of issue/replacement frequently gives rise to problems. Recipients of SOP documents were not defined and consequently not everyone received replacements; additional copies were made from in-use copies, again making it impossible to identify all recipients. The SOP supplier (usually QA) should ideally issue numbered copies to identified recipients and copying of distributed SOPs should not be permitted; this can be monitored for by printing the number (or other confirmation) in a different color so that photocopying would be obvious. With the advent of computerized information and management systems, current SOP documents could be automatically available to everyone, thereby minimizing the potential for use of outdated procedures. A procedure is still required to alert people that an SOP has been revised. It is appropriate for QC to retain copies of superseded procedures. These can be useful reference documents in the event of a problem arising later.

The master batch record, which provides full details of how a product is to be manufactured, could be considered a very important SOP. As with all SOPs the amount of detail provided should be adequate to assure that different individuals will be consistent in following the process. This not only enhances the potential for consistent product quality, but it also allows more effective evaluation of the causes of any quality deviations and provides a firm basis for process optimization. It has been commented that American operators have a tendency to apply their own individual variability and preferences to processes, thereby making it difficult to evaluate deviations or to make improvements. Conversely, the Japanese tend to follow the process implicitly until an improvement is introduced.

The procedures for production and process control are to be reviewed and approved by quality control. This does not mean that QC are to be considered expert in each area of the operation. For example, the production document would normally be reviewed initially by production and/or technical services; the role of QC would be to confirm this review by a responsible person and to further review the document for possible adverse impacts on quality and safety. When reviewing the production and process control documentation it will be essential to check that:

- a. The various requirements referenced in the CGMP regulations (especially the other subsections of Subpart F) have been adequately addressed.

- b. The documents are in compliance with the relevant sections of any NDA and ANDA.

The FDA is currently reevaluating approval requirements with respect to production changes. The objectives are to reduce the work load at the FDA, harmonize via ICH, and allow quicker implementation of changes. The status is somewhat confused by the ICH approach, which primarily focuses on stability requirements while the FDA also addresses levels of approval (Annual Report, Change Being Effectuated, Prior Approval). Due to lack of consensus between the ICH parties, the ICH project is currently on hold. The situation is further compounded by the issuance by the FDA of two similar but not identical proposals in November and December 1994 (see Suggested Readings 16 and 19). The November guideline developed by the Scale-Up and Post Approval Change (SUPAC) Expert Working Group of the Chemistry Manufacturing Controls Coordinating Committee of the Center for Drug Evaluation and Research was limited to immediate release solid dosage forms. Guidelines on other dosage forms will be issued.

The SUPAC document proposed defined procedures and required supporting data for (a) changes in excipient quality and quantity, (b) changes in site of manufacture, (c) scale-up, and (d) equipment and/or process changes. While this is a move in the right direction, it is not far enough. For most changes to an approved NDA/ANDA it ought to be sufficient to define the supporting data requirements (stability, validation, comparative analysis, dissolution profiles) and allow immediate implementation. The adequacy of the data could then be checked by FDA field investigators. The delays involved in obtaining FDA approval for changes (which can take up to 24 months) can have adverse impact on the industry and on the consumer. For planned changes the impact may primarily be financial—the use of an improved, less expensive process or of an alternative cheaper source of material may be delayed. But a bigger issue is the delayed FDA approval when changes are unexpected—a supplier is unable to provide further material or a piece of equipment becomes nonfunctional. These could result in nonavailability of product for the end user.

The FDA approach in this area of change tends to illustrate the FDA suspicion of industry that if not tightly controlled it will behave unprofessionally. Unfortunately, there have been a few examples to support this attitude. With respect to a bulk drug, prior FDA approval is required for a change in solvent or route of synthesis, for a different production facility if it involves changes in equipment types or the facility has not been inspected by the FDA in the previous 2 years, relaxation of limits, deletion of specification or new analytical methods.

- c. There are appropriate supporting data such as process validation, analytical method validation and product stability.

- d. The document does not affect the “grandfather” status of old drugs.
- e. The reasons for any proposed changes from previous procedures are clearly defined and supported.
- f. The appropriate functions, such as production and technical services have been reviewed and signed off.
- g. The procedures are compatible with any compendial requirements (such as USP). Part 314 does allow for compliance with compendial changes to be included in the annual report.

The effectiveness of any procedure is closely related to the ability of those responsible for its initiation and operation. The QC function should record the performance of individuals who have review responsibilities. This will provide useful background information on which to base any additional training needs. In the event that poor performance does not improve adequately after training it may be necessary to exclude an individual from the review process. The same approach should be used to monitor the performance of all employees with respect to every important procedure. QC cannot adequately perform its overview responsibility role without such an approach.

Having provided written and approved procedures, the next stage is to ensure that they are followed. This involves training and verification steps. Employees must be given training in all relevant procedures. This should include an understanding and awareness of the purpose of the procedures and why they need to be followed. As with all training, it should be confirmed that the employee has actually learned the relevant information and there should be a record of the successful completion of the training. Next comes the verification step. A combination of some, or preferably all, of the following approaches provides data on compliance.

1. Regular monitoring of compliance by supervisors and managers as they do their daily work. This can be informal but it allows immediate identification and correction of potential compliance problems. It further demonstrates to employees that management does consider compliance to be important.
2. A more systematic review of compliance can also be performed by supervisors and managers on a less frequent basis—perhaps monthly. This again would be done by comparing actual activities with written procedures. This more systematic approach ensures that no department, process or shift is ignored.
3. Quality assurance, along with departmental management, perform an audit of each function. A written report should be issued and if possible any deficiencies should be quantified thereby allowing trends to be monitored. Quantification can be relatively simple, such as classifica-

tion of deficiencies into critical, major and minor and recording the number and percentage of each. Alternatively a numerical weighting system can be used. Management would be expected to evaluate the audit report, identify the root causes of any noted deficiencies and to specify appropriate corrective action.

4. Independent audit from outside of the plant adds another level of review. This is similar to 3 above but may involve personnel from another facility or corporate staff. Also included in this category are regulatory audits such as those by the FDA. One effective approach to independent audit is to adopt the process approach as used by the Malcolm Baldrige National Quality Award. This has the advantages that it can be focused toward specific processes, allows clear identification of causes of deficiencies, gives credit for positive achievement, identifies centers of excellence, and can provide numerical trend data that can stimulate top management to action.
5. The routine quality assurance check of batch records also provides basic information on compliance. This should also be used to review deviation frequency, evaluation, and corrective action and to confirm compliance with FDA registration data.

It should be emphasized that if the data generated in 1, 2, and 5 above are used to identify and correct basic problems, then the audits described in 3 and 4 should simply provide confirmation of compliance. Traditionally, independent audits (4 above) were used to identify areas of noncompliance. Since they are performed relatively infrequently and can only examine small parts of a production operation, they are ineffective as a basis for identifying all noncomplying activities. The emphasis should be on self-evaluation (1 and 2), which is more likely to be successful than the utilization of a police-type activity. The persistent finding of noncompliance issues by QA should signal that management are not giving enough attention to the subject, that training is not adequate or that procedures are too complex. QA should then work with the appropriate managers to identify the causes and to initiate corrective action.

In order to encourage self-audit, the FDA had agreed not to ask for copies of internal audit reports (Compliance Policy Guides 7151.02). They may, however, ask for evidence that audits are performed. Also, in the event of litigation requests may be made to see such records. Recently some FDA investigators have begun to request copies of internal audit reports—reputedly to confirm that the audits have been performed. This could discourage companies from using comprehensive reports that identify deviations, thereby providing investigators with a potential source of 483 citations. In a professional but nonantagonistic FDA–industry environment the sharing of this audit data could be mutually bene-

ficial. By accepting that a company had identified and was correcting deficiencies, an investigator could focus on the improvement activities or other areas or even other companies.

The computerization of process documentation can improve the effectiveness of compliance. The production system can be designed so that one stage has to be completed and any relevant data entered into the computer before the next stage can be initiated. Process control limits can also be included and any atypical results can be made to automatically initiate managerial review. The subject of validation of computer systems is included in [Chapter 5](#).

It would be difficult, if not impossible, to draft an operating procedure that will meet all circumstances. On occasion, deviations from the defined procedure will occur or will be necessary. In such instances the deviation should be clearly recorded. Where the deviation was deliberate, the rationale should be explained. Whether deliberate or accidental, the responsible individuals should review the event to establish the potential impact on, and disposition of, the resulting product. If appropriate, the procedure may be resubmitted into the approval system in order to be permanently incorporated into the master documentation. Obviously in an effective operation deviations should not be a common occurrence.

Section 211.100(a) requires the review and appraisal of changes to production and process control procedures. However, this review and approval should be considered in the broader concept of change control.

CHANGE CONTROL

A consistent achievement of product quality is dependent on the availability of defined/approved/validated procedures and the application and adherence to these procedures by trained personnel. In the event that any change is to be introduced into the production operation, it is important to evaluate its potential impact and where necessary provide appropriate evaluation and/or actions. The procedure that controls change is, not unexpectedly, called “change control.” This should be a defined, proactive management system that facilitates a review of any proposed change and monitors the impact of the change. The system should be fail-safe by preventing changes that could adversely affect product quality or conflict with registration or regulatory requirements. The procedure should have identified ownership with responsibility for maintenance, monitoring, and improvement of the procedure along with training. Change control should include changes to raw materials, packaging components, labeling, expiration dating, formulation, production process, production equipment (including major maintenance), critical plant systems, facilities, computerized systems, specifications, and test methods.

The procedure will involve multiple disciplines including sales and marketing, medical, legal, manufacturing, regulatory affairs, R&D, technical services,

and maintenance, as well as QC/QA. Not all functions will need to be involved with all changes. The evaluation of the change, which must be documented, will include:

- Clear definition of the proposed change with the reason for the change.
- Identification of potential impact and the evaluations to be performed, such as accelerated stability, revalidation, retraining.
- Regulatory impact (all countries involved) and approvals required.
- Schedule for implementation.
- Definition of who needs to approve the change and a record of their concurrence.
- Postintroduction review to confirm that the change did not have any adverse impact.

The change control procedure is possibly the most important SOP in a plant operation. It is also one of the most broad ranging and most complex. Consequently the management of the process must be delegated to someone with the necessary knowledge and skills to understand and manage this complexity. In larger facilities there may be separate change control procedures for different types of change. However, QC/QA should confirm that each meets the needs of the operation.

Evaluation of change control should be part of the QA plant audit.

§211.101 CHARGE-IN OF COMPONENTS

Written production and control procedures shall include the following, which are designed to assure that the drug products produced have the identity, strength, quality, and purity they purport or are represented to possess:

(a) The batch shall be formulated with the intent to provide not less than 100 percent of the labeled or established amount of active ingredient.

(b) Components for drug product manufacturing shall be weighed, measured, or subdivided as appropriate. If a component is removed from the original container to another, the new container shall be identified with the following information:

(1) Component name or item code

(2) Receiving or control number

(3) Weight or measure in new container

(4) Batch for which component was dispensed, including its product name, strength, and lot number

(c) Weighing, measuring, or subdividing operations for components shall be adequately supervised. Each container of component dispensed to manufacturing shall be examined by a second person to assure that:

- (1) The component was released by the quality control unit.
- (2) The weight or measure is correct as stated in the batch production records.
- (3) The containers are properly identified.
- (d) Each component shall be added to the batch by one person and verified by a second person.

The requirement to “formulate with the intent to provide not less than 100% . . . of the active ingredient” requires some explanation. This certainly makes it unacceptable to add only sufficient material to meet the lower end of the specification, although no reputable manufacturer would ever use this approach. It is not the intention of the regulations to require calculation of an exact amount of active ingredient based on the assay value of the material for each batch of product. Most active ingredients show assay results that are not exactly 100%. With inherent errors in analytical methodology in the order of 1–2% it is not possible to precisely determine the “true” assay value. Consequently it is acceptable to use material that is within the acceptable specification without specific adjustment to accommodate batch analytical variations. This may not be adequate for materials with a significant, and variable, loss on drying. When it is necessary to calculate a specific quantity this requirement should be specified in writing by QC and not be the subject of telephone or other verbal communication. For a product that is known to show some inherent loss of potency during the production process, it may be advisable to take the assay value into account for each batch. It may also be necessary to add an overage to allow for this potency loss.

The dispensing step is a critical stage of the manufacturing operation. It ensures that the right amounts of the correct material, released by QC, are allocated to the specified batch of product. The labeling of the component containers ((b)(1)–(4)) makes the later checking at production usage more effective. As written, §211.101(b) could be interpreted that it is only necessary to include the labeling requirements if material is transferred from its original container. However, such a literal interpretation would be illogical and would weaken the system since the original container will not reference the drug product name, strength, or lot number.

The dispensing operation also provides an ideal opportunity to visually examine containers for damage, and contents for atypical appearance or foreign matter. Dispensing operators should be made aware of the importance of this role to the achievement of quality standards.

The requirement that “each container of component dispensed to manufacturing shall be examined by a second person” (§211.101(c)) is usually interpreted to mean that a second person should be available in the dispensary to perform this duplicate check. Several alternatives would also appear to achieve the same result. A single check could be performed in the dispensary with the second check being done on receipt by production. With some manual systems the dispensary

label can be removed at the production stage and become part of the batch record. Either routinely, or in the event of a problem, the individual labels can be examined. A second effective alternative is the replacement of the second check by the availability of a suitable computer system. Computer systems are available that will prevent the weighing of an incorrect or unreleased component; they will also disallow completion of the dispensing step if the amount of material being weighed is outside of the defined operational tolerances. Such systems can also be designed to allow only designated individuals to weigh out specified materials, as in the case of controlled substances or materials to which an individual employee may be allergic. Another alternative is the use of bar codes, applied to the incoming materials, and the monitoring of their use and disposition throughout the production operation by scanning equipment. These systems provide much more effective control over the dispensing function than does a second human check and should be introduced whenever possible. An added advantage of such systems is that they allow immediate reconciliation; in the event that a raw material being weighed did not correlate with the records, the dispensing could be automatically put on hold until an investigation had been initiated.

The requirement for a second person, in production, to verify the addition of components to a process is subject to the same argument as that used above for dispensing. For example, if component containers are provided with a bar code, the scanning of this bar code on addition to the batch would provide the assurance required.

The overall topic of double-checking has been raised by industry with the FDA. As indicated above, the alternative approaches are much more effective and provide a higher level of assurance that specific actions have been performed. This is an excellent illustration of the CGMP regulation being too detailed and too restrictive. Unfortunately, the alternative approaches are not acceptable to the FDA without a change in the regulations—which tends to take a considerable time.

§211.103 CALCULATION OF YIELD

Actual yields and percentages of theoretical yield shall be determined at the conclusion of each appropriate phase of manufacturing, processing, packaging, or holding of the drug product. Such calculations shall be performed by one person and independently verified by a second person.

Theoretical yield is defined in Section 210.3(b)(17) as the maximum quantity that could be produced, based on the quantities of components used, in the absence of any loss or error in production. Theoretical yield consists of the summation of the weights of all raw materials entering the production cycle. For

granulations, powders, and tablet coatings, an amount equal to evaporated solvent should be subtracted.

Based on historical data an acceptable range for actual yield at each appropriate stage can be calculated. This range is sometimes set so that 95% of batches produced will fall within the range when the process is operating correctly. The purpose of this is to alert management to atypical situations that may require investigation. Low yields may not only signal potential problems but may also indicate opportunities for process improvement with subsequent cost benefits. Process losses can occur for a variety of reasons including dust extraction, spillage of components or product, machine losses such as in compression, machine adjustments, samples, or residue in equipment. The regulations again require that a second person verify independently the yield calculations. The availability of an automated and validated calculation procedure would seem to be a viable, and preferable alternative.

§211.105 EQUIPMENT IDENTIFICATION

(a) All compounding and storage containers, processing lines and major equipment used during the production of a batch of a drug product shall be properly identified at all times to indicate their contents and, when necessary, the phase of processing of the batch.

This regulation requires that all equipment and lines always bear a label showing their status: clean, to be cleaned, or with the product name and lot number and, if necessary, the phase of processing. If equipment is permanently installed and used for only one batch of product at a time, it may be acceptable to status label the complete suite. This approach is economical with respect to the application of status labels but individual pieces of equipment tend to be cleaned separately. It may still be advisable to status-label individual items after cleaning to ensure that no uncleaned equipment is allowed to be used.

Some recording system should be introduced to allow back reference to the status data in the event of a problem. Alternative approaches include the retention and filing of status labels or the use of log books. The former may be preferred since it is a record of the actual documentation rather than a transcription into a log book.

The labeling of containers of material in-process should clearly define the product, batch number, and state of processing (e.g., granule, bulk tablet, etc.). Where several containers are involved they should be numbered sequentially. This is of particular value in the event that a problem is later identified and needs to be investigated.

Where materials are to be transported to other sites, it may also be appropriate to place a label inside the container as an extra precaution in case the outer label gets lost or defaced.

(b) Major equipment shall be identified by a distinctive identification number or code that shall be recorded in the batch production record to show the specific equipment used in the manufacture of each batch of a drug product. In cases where only one of a particular type of equipment exists in a manufacturing facility, the name of the equipment may be used in lieu of a distinctive identification number or code.

The intent of this subsection is to allow identification, at some future date, of the specific piece of equipment involved. This is particularly appropriate where a manufacturer may have several different pieces of the same equipment, which may not behave identically. If the manufacturer has only one piece, then reference by name alone will suffice.

§211.110 SAMPLING AND TESTING OF IN-PROCESS MATERIALS AND DRUG PRODUCTS

(a) To assure batch uniformity and integrity of drug products, written procedures shall be established and followed that describe the in-process controls, and tests, or examinations to be conducted on appropriate samples of in-process materials of each batch. Such control procedures shall be established to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product. Such control procedures shall include, but are not limited to, the following, where appropriate:

- (1) Tablet or capsule weight variation
- (2) Disintegration time
- (3) Adequacy of mixing to assure uniformity and homogeneity
- (4) Dissolution time and rate
- (5) Clarity, completeness, or pH of solutions

(b) Valid in-process specifications for such characteristics shall be consistent with drug product final specifications and shall be derived from previous acceptable process average and process variability estimates where possible and determined by the application of suitable statistical procedures where appropriate. Examination and testing samples shall assure that the drug product and in-process material conform to specifications.

(c) In-process materials shall be tested for identity, strength, quality, and purity as appropriate, and approved or rejected by the quality control unit, during the production process, e.g., at commencement or completion of significant phases or after storage for long periods.

The first stage in establishing appropriate process control criteria is the identification of the key factors which impact on quality and the evaluation of acceptable operational ranges for these. This is referred to as process validation.

PROCESS VALIDATION

The FDA in “Guidelines on General Principles of Process Validation” defines process validation as “establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality characteristics.” The designing of quality into a product and its production processes, coupled with supporting validation data, increases the potential for consistently achieving quality standards and reduces dependence on both in-process and end-product testing.

When the concept of validation was introduced the FDA recognized two approaches: retrospective and prospective. Retrospective validation involved an in-depth evaluation of a large number of consecutive batches of product to correlate processing conditions and analytical results. Provided materials quality and processing conditions are adequately controlled and reported, this approach can clearly demonstrate whether a process is under control. The range of processing conditions resulting in satisfactory product quality can then be used to define acceptable ranges in master production documentation. The advantage of this approach was that it allowed identification of processes that were in control without the need for new additional testing. For those processes that yielded variable product quality, further work was required to make the processes reproducible. For new products this approach is not acceptable, since many batches would need to be produced before sufficient data were generated—this would mean that in the interim period product quality had to be assured by a heavy reliance on test results. A further disadvantage of the retrospective approach was that in many instances the process variables were inadequately controlled or reported, making the evaluation suspect. The FDA now expects validation to be prospective—completed before commercialization. However, as validation requirements began to be expected for bulk pharmaceutical chemicals, many companies reactivated the retrospective approach—with the same benefits and constraints noted for dosage forms.

There is another potential situation: a new product or process is to be used but it is impracticable to complete the validation before going to market. Some examples include an urgent need to change a process because of equipment failure, the need to change batch size because of unexpected sales volumes, the need to change supplier of a key material due to unforeseen supply problems, changes associated with a low-volume product where three validation batches would equate to several years of stock. In these circumstances it would seem practical to perform only critical validation studies prior to marketing, coupled with exten-

sive in-process and finished product testing to confirm the consistency of product quality. The validation would be completed on other batches as they were required. The FDA has been unwilling to accept this approach and has rigidly adhered to the concept of three validation batches before commercialization. This would appear to be a good example of where good science should be allowed as an exception to regulatory expectations.

The subject of process validation gained new attention by the introduction of the FDA Compliance Program 7346.832 in 1990. The subject was Pre-Approval Inspections/Investigations (PAI). The impact of PAI on the entire compliance program has been so significant that a separate chapter has been devoted to the subject (Chapter 19).

Prospective validation involves several stages: product and process design; equipment installation and operational qualification (IQ and OQ); services qualification; process performance; performance evaluation (Figure 1).

For each phase of validation, protocols should be compiled and approved by the relevant functions. These protocols should clearly define the work to be performed and the acceptance criteria. On completion the data should be evaluated against the acceptance criteria and where acceptable the validation approved.

During the product development phase there should be interactive involvement of all appropriate technical functions, usually R & D, engineering, manufacturing, technical services, and quality control. This should ensure that the product as designed by R & D has a high probability of manufacturing success/consistency when transferred into the production operation. This technology transfer process needs to be clearly elaborated with responsibilities and interactive collaboration defined. Since the required involvement by plant operations usually occurs many months (sometimes years) before the product is approved for commercial launch, there can be reluctance for this involvement. However, the potential benefits should override any reluctance. An example that illustrates this point

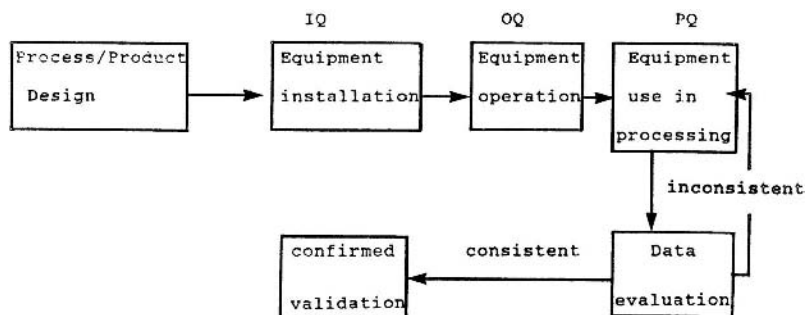


Figure 1 Validation stages.

was a situation where R & D developed a tablet product that could not be produced without significant capital expenditure in the plant to provide special environmental conditions—the equipment was on a long lead time, which delayed introduction of the product. Earlier involvement of production personnel could have encouraged modification of the product or process or, alternatively, the required equipment could have been ordered earlier. Early involvement of QC can also be used to evaluate the robustness of analytical methods.

When new equipment is purchased, the first step on receipt is to ensure that what is delivered is what was ordered and then to confirm its proper assembly and installation. This is followed by operation of the equipment to confirm that it does function in accordance with the design and purchase specifications. This includes such parameters as speeds of mixers, heat distribution of ovens, and calibration of monitoring instruments.

The specific unit operations are supported by services such as water, electricity, environmental air, and compressed gases. These too must be qualified. This will involve installation/operational qualification, which includes as-built drawings; weld certification for pipework; airflow volumes, pressure differentials and particulate levels (viable and nonviable); microbial evaluation of water quality; effectiveness of filters (air, water, gases); validation of computerized systems for environmental control; and temperature and humidity controls for HVAC systems.

When the facilities, the supporting systems, and the equipment are qualified, it is time to qualify (validate) the specific production processes.

The process validation protocol should include:

- a. The facilities, services, and equipment to be used.
- b. The key variables likely to impact on quality. These are usually identified during the product development process or from experience with similar products.
- c. The range of conditions to be evaluated for each variable. The range of conditions to be evaluated should extend beyond the anticipated operational ranges of the process. It has been suggested that the validation ranges should extend to the point where the process fails—“worst case.” There would seem to be no need for this provided operational ranges are maintained inside the values evaluated during validation.

The possible interrelating effects of different process variables could require an extensive number of evaluations. The number of experiments can be reduced by the application of suitable statistical methods—design of experiments.

All test equipment, gauges and recorders used in the validation process should be calibrated immediately prior to and after each validation experiment.

- d. The samples to be taken; location, size, number, and frequency.
- e. The tests to be performed and the methodology to be used. Analytical methods must be validated otherwise any data generated will be of doubtful value.
- f. The number of replicate process runs to be performed.
- g. The acceptance criteria.
- h. Details of who must review the data and where it is to be retained for permanent reference.

In a legal case involving Barr Laboratories in 1993, the judge issued rulings of which some apply to validation. Although these rulings should apply only to Barr Laboratories, the FDA advised their investigators to incorporate these as FDA requirements. These rulings included:

- For solid dosage validation the granule or powder mix must be evaluated for uniformity in addition to the tablets/capsules themselves.
- Sample size from the blend should be small and should resemble the dosage size, preferably not more than three times the active ingredient dosage size.
- Compositing of samples should not occur.
- Samples should be representative of all parts of the batch. This means that samples should be taken from places that might be problem areas.
- Sampling from drums of blended powder or granule should only occur if it can be demonstrated that this was representative.
- Concurrent and prospective validation requires at least three consecutive batches.
- Particle size distribution specifications should be defined and evaluated.

While many of the rulings by Judge Wolin represent good scientific judgment, it does not seem appropriate that a judge should be defining CGMPs.

Revalidation. A system must be established which initiates a review of the need for revalidation whenever there is a change in the equipment, facilities, process, services, formulation, or source of components. Additionally because some changes may be made without notification it may be advisable to consider revalidation either at predetermined frequencies or if some atypical product behavior is noted—this could be according to a reduced level protocol.

On completion of process validation it is then possible to define the operational parameters for the process which if followed should assure compliant product. The batch card defines these operational parameters and the in-process controls provide confirmation that the process has remained under control. The use of statistical control charts will identify trends and the need for any process adjustment; they will also make it easier to pinpoint and contain substandard product if a process goes temporarily out of control. An important element in the

validation/revalidation process is the evaluation of process data from production batches. If process modifications are required to keep the quality consistent or if reworking/rejections occur, then it is possible that the process has not been adequately validated. Some process variables have not been fully identified and revalidation may be required (Figure 1).

It has been common practice for production personnel to perform many of the in-process tests, usually with QC repeating some of these at less frequent intervals. The current trend in managing quality is to transfer accountability for quality to the individual performing the job. This is much more likely to be successful than by the operation of a police-style QC department trying to play “catch-it.” However, QC still do retain the overall responsibility of ensuring that released product meets the required standards. Consequently operators must be made fully aware of their role and its potential impact on the consumer and the company; they must also be provided with suitable equipment and training and be supported, and audited, by QC. Where possible, equipment for in-process testing should be simple to use, robust, and of a recording type.

(d) Rejected in-process materials shall be identified and controlled under a quarantine system designed to prevent their use in manufacturing or processing operations for which they are unsuitable.

Since production processes are designed and operated to produce complying material, a rejection should be a cause for concern. An investigation of the problem must be initiated and must be of sufficient depth to identify the root cause and not just the symptom. Unless the real basic cause is identified, the problem is likely to reoccur. This is illustrated by an example.

A bulk solution was assayed at 80%; the analyst reassayed and again obtained 80%. The batch was adjusted to 100% and reassayed by another analyst at 120%. This latter value was confirmed. After investigation the cause was stated to be misinterpretation of the analytical method by a new analyst for whom additional training was initiated. This would not prevent a recurrence. Further evaluation would have shown that the root cause was that the system for handling atypical results was inadequate. It did not require an investigation or involvement by a supervisor or manager, nor did it require the repeat analysis to be performed by another analyst.

Identification of root cause should be followed by appropriate corrective action to prevent a future reoccurrence. In the example above, this would involve rewriting the procedure for dealing with atypical results. During the investigation it should be established whether there has been a previous similar occurrence; this could indicate that the root cause probably had not been identified on the earlier occasion.

Having identified the cause of the problem, the disposition of the affected material must be addressed. Rejected materials need not necessarily be destroyed.

The material may be suitable for reprocessing (see §211.115). While retained in a reject status, materials should be controlled, either physically or by way of a system, to preclude their inadvertent further processing. Rejected materials should be disposed of as quickly as possible to further minimize risk. FDA investigators also tend to visit the reject area and use the information obtained to identify potential GMP deviations.

§211.111 TIME LIMITATIONS ON PRODUCTION

When appropriate, time limits for the completion of each phase of production shall be established to assure the quality of the drug product. Deviation from established time limits may be acceptable if such deviation does not compromise the quality of the drug product. Such deviation shall be justified and documented.

The main purpose of this regulation is to indicate that certain processes are sufficiently sensitive that time limits need to be established for their completion. This could be especially important for:

- a. Material vulnerable to microbial attack. Bulk injections are usually required to be filled into the final container within 48 hours; otherwise any microbial contamination could result in high levels of pyrogenic material.
- b. Materials subject to oxidation may be protected with nitrogen. Effective nitrogen protection may be difficult at the bulk stage; also, failure of the nitrogen system could result in batch rejection.
- c. Tablet granulations or other bulk solids may absorb or release moisture on storage, making them more difficult to process or even accelerating decomposition. Batch records should clearly indicate any time-scale restriction and dates and times should be recorded. In the event that a defined time-scale is exceeded, this may not necessarily result in batch rejection. But an investigation must be initiated to identify the cause and the possible implications of the changed time-scales. Only if adverse effects are unlikely can the material be used. For example, if pyrogenicity is the concern, this could be measured and if results are not atypical it may be possible to use the material.

Extension of established and validated time scales may be used as a basis for extending these times. For example, if an accepted holding time of 48 hours has been extended to 60 hours with no adverse impact, it may be possible to change the accepted holding time to 60 hours. In most instances data from more

than one such extension will be required before a permanent change can be implemented.

Another important timing parameter relates to the actual time-scales for unit processing such as mixing and drying. This is normally addressed at the process validation and process control stages.

§211.113 CONTROL OF MICROBIOLOGICAL CONTAMINATION

(a) Appropriate written procedures, designed to prevent objectionable microorganisms in drug products not required to be sterile, shall be established and followed.

Every day the human body is invaded by countless numbers of microorganisms, which are found in the food we eat, the air we breathe, and the water we drink. Consequently, for most products other than injections, there is no need for sterility. For products that are not required to be sterile, the presence of microorganisms could still constitute a problem. Certain microorganisms are associated with human illness and should be absent. The United States Pharmacopeia suggests that natural plant and animal products and some materials of mineral origin be tested for freedom of *Salmonella* species, which may be inherent in their source; oral suspensions and solutions be tested for freedom from *Escherichia coli*; products for topical application be tested for freedom from *Pseudomonas aeruginosa* and *Staphylococcus aureus*.

Some products may also be prone to microbial degradation resulting in loss of active ingredient or breakdown in physical characteristics, such as emulsions. In such cases it may be necessary to have a specification for total viable microorganisms. The end use of the product may also make it appropriate to have such limits: for example, for product used around the eyes or on mucous membranes.

The procedures and conditions required to assure adequate microbial quality will vary according to the specific products but are likely to include some, or all, of the following:

1. Microbial monitoring of potentially susceptible raw materials. This may require special negotiation with the supplier if a microbiological specification is not a normal requirement for his other customers.

Current practices involve the setting of microbial specifications for materials of natural (animal, vegetable or mineral) origin, those likely to support microbial growth and materials to be used in product formulations with rigorous microbial specifications—such as injections. However, a USP *Pharmacopeal Preview* article in 1992 did propose microbial specifications for all pharmaceutical raw

Table 1 Assignment of Microbial Count Limits for Raw Ingredients, Excipients, and Drug Substances (on the Basis of the Origins of These Materials)

Material type	First-tier testing total bacterial count/g		Second-tier testing	
	Microbial alert level (X)	Microbial action level (5X)	Yeast and mold count/g ^d	Absence of indicator organisms ^e
Synthetic ^a	200	1,000	100	<i>Escherichia coli</i> <i>Staphylococcus aureus</i> <i>Pseudomonas aeruginosa</i>
Natural ^b	1,000	5,000	500	<i>Salmonella</i> <i>Escherichia coli</i> <i>Staphylococcus aureus</i> <i>Pseudomonas aeruginosa</i>
Material that can be decontaminated ^c	20	100	10	<i>Salmonella</i> <i>Escherichia coli</i> <i>Staphylococcus aureus</i> <i>Pseudomonas aeruginosa</i>

^a Nonbiological/nonmineral materials.

^b Plant, animal, or mineral materials (e.g., gums, sugar, gelatin, starches, hormones, talc, silica, etc.).

^c Values indicated are for materials following decontamination.

^d When the bacterial count is >X but ≤5X/g, the yeast and mold count is performed.

^e Tests for the absence of indicated organisms when bacterial count is >X but ≤5X/g.

materials (Table 1). The rationale and logic underlying the proposal would appear to be flawed. It would seem illogical to require synthetic materials to have a lower microbial count than materials of natural origin. These latter materials, with their higher counts, are considered to cause no health hazard; therefore, why impose more stringent limits on synthetic materials? The same comment can be applied to materials that can be decontaminated, where a lower specification was proposed. At this stage the proposal has not progressed.

2. Equipment sanitation procedures that have been proven effective especially for any specific known deleterious or objectionable microorganisms.
3. Processing conditions that minimize the potential for microbial growth.
4. Environmental control including covers over equipment; laminar flow at susceptible points, wearing of protective clothing such as gloves and masks, clearing filling lines at breaks.
5. Formulations to include preservatives.

In 1992 the USP published guidelines on microbial limits for nonsterile products (Table 2). While there may be some need for limits for liquid products, and most reputable companies already apply their own limits, there would seem to be less value for solid oral dosage products. As far as we are aware, microbial contamination has not been a problem except for products involving materials of natural origin. The USP proposal did suggest that with effective raw material and process control coupled with an acceptable historical database it should be possible to revert to periodic rather than routine testing. This does, however, ignore the amount of work to develop methodology and to establish the database initially. In an environment where health care costs are constantly under scrutiny, additional tests or tighter standards should not be proposed unless there are valid scientific, health, or safety reasons.

(b) Appropriate written procedures, designed to prevent microbiological contamination of drug products purporting to be sterile, shall be established and followed. Such procedures shall include validation of any sterilization process.

Sterile products are manufactured using either terminal sterilization or aseptic processing. The level of sterility assurance is significantly higher with terminal sterilization; autoclaving at 121°C can easily result in a 10^{-6} microbial survivor

Table 2 Assignment of Microbial Count Limits for Nonsterile Finished Dosage Forms (by Route of Administration)

Route of administration	Bacterial count limit (cfu/g or ml)	Yeast and mold count (cfu/g or ml)	Absence of indicator organisms
Inhalants	10	2	<i>Escherichia coli</i> <i>Staphylococcus aureus</i> <i>Pseudomonas aeruginosa</i> <i>Salmonella</i> ^a
Topical/vaginal/ rectal/nasal/otic	100	10	<i>Escherichia coli</i> <i>Staphylococcus aureus</i> <i>Pseudomonas aeruginosa</i> <i>Salmonella</i> ^a
Oral—liquid	500	50	<i>Salmonella</i> <i>Escherichia coli</i> <i>Staphylococcus aureus</i>
Oral—solid	1,000	100	<i>Salmonella</i> <i>Escherichia coli</i> <i>Staphylococcus aureus</i>

^a If the dosage form contains material of plant, animal, or mineral origin.

probability whereas aseptic processing tends to result in the order of 10^{-3} . Because of these significant differences in assurance levels, terminal sterilization should be the method of choice. Some products cannot withstand the temperature conditions of autoclaving, the ingredients may be heat labile or the package may be physically affected by the pressure changes (e.g., prefilled syringes), and aseptic processing may then be necessary. A useful compromise situation is a combination of aseptic processing with some level of heat treatment that could effectively kill off vegetative organisms without adversely affecting chemical stability or physical integrity.

The subject of aseptic processing versus heat sterilization or the compromise of aseptic plus some heat treatment can be very complex, especially for those products that have some degree of heat lability. What conditions should be used to evaluate heat treatment that are less rigorous than typical sterilization conditions? The possible permutations of temperature and time are almost limitless. Also, what are the relative benefits/disadvantages of aseptic processing with low levels of degradants and some heat treatment with higher levels of sterility assurance but also higher levels of degradants? Unless clear guidelines are agreed on or companies are allowed to make their own judgmental decisions, there will be regulatory chaos with higher development costs and delays in approvals.

Whichever process is used, the probability of having a nonsterile unit will be extremely low. Consequently, assurance of sterility cannot be demonstrated by testing a limited number of samples. For example, when sterility testing 10 units, lots with 0.1% contaminated units could be passed as sterile 99 out of 100 times. Increasing the sample size to 100 still leaves a 91% chance of passing a contaminated batch. Also, if the sample size is increased the potential for false-positives also increases. This then places a greater emphasis on the need to validate the sterilization process and to ensure that the defined process is followed for every batch of product. The key parameters to be evaluated for the different types of sterilization are outlined below, but whichever process is used, the same basic steps outline previously for process validation are also to be included: product/process design, equipment qualification, services qualification, process performance, and revalidation. Validation of heat sterilization (dry heat or autoclave) includes:

1. Heat distribution within the empty sterilization chamber.
2. Heat penetration within the units of product for the various loading cycles to be used.
3. Lethality calculations based on kill of known numbers of resistant bacteria or spores, usually *Bacillus stearothermophilus* spores placed in units that receive the least heat treatment.
4. Bioburden data showing the numbers and types of organisms, with

particular reference to resistivity, likely to result from the components and the process prior to sterilization.

5. Perform studies outside the ranges of conditions that will routinely be used for sterilization cycles.

Of relevant interest is an FDA Policy Guide provided in [Chapter 10](#) in reference to Parametric Release/Terminally Heat Sterilized Drug Products

VALIDATION OF ASEPTIC PROCESSING

1. Treatments of product components and processing equipment to remove particulate matter, sterilize, and depyrogenize are critical to effective aseptic processing. This will include ampoules, vials, stoppers, filters, intermediate storage vessels, tubing, filling equipment, gowns, masks, and gloves. The processes for each of these must be validated.
2. Environmental qualifications must include:
 - a. Air quality. At point of use (e.g., filling) air should be supplied by HEPA-filtered laminar flow air at about 90 feet per minute and with a pressure differential to adjacent areas of 0.05 inches of water. Nonviable particle counts should be less than 100 per cubic foot equal to or larger than 0.5 micron (Class 100); viable particles should be not more than one colony forming unit per 10 cubic feet.

Away from the critical filling area, where product is not exposed to the environment, less stringent requirements are necessary but must still be controlled in order to minimize the bioburden load. The Class 100,000 (not more than 100,000 particles per 0.5 micron or larger and not more than 25 colony forming units per 10 cubic feet) should be adequate. Air filter integrity and efficiency testing should be included.

- b. People. The presence of people in an area or room will impact on air quality. The validation study should include the maximum number of people expected to be present at any time during the process. Other people-related activities to be examined would be training programs especially with respect to microbiological understanding, aseptic techniques, and gowning techniques. The effectiveness of these techniques can be evaluated by the use of swabs, contact plates and touch plates.
3. Time limitations. Liquid preparations and wet components are prone to microbial multiplication, including the possibility of microorganisms passing through filters. Maximum time frames for key steps need to be confirmed.

4. Product filtration. The filtration system used to “sterilize” the drug product, usually 0.22 micron, should be challenged using a suitable small organism, usually *Pseudomonas diminutia*. The number of organisms used in the challenge will be in excess of the maximum bio-burden levels measured in unfiltered solutions.
5. Media fills. The overall effectiveness of the aseptic process is then validated using liquid media fills.
 - a. Initially three media fills are considered desirable.
 - b. A minimum of 3000 units should be filled to provide a 95% probability of detecting contamination at a level of one in one thousand.
 - c. Each shift and each employee used for aseptic processing should be included in the validation runs.
6. Revalidation. As with any process, revalidation should be considered whenever there is a change in the product, components, process, facility, equipment or people. Additionally, since the aseptic process is so people dependent, regular revalidation is essential. This routine revalidation should normally be performed every six months on each different type of process and for each shift; every operator should be included in a revalidation at least every 12 months.

The routinely collected data on bioburden levels and environmental conditions will also serve to confirm that the process is being maintained under control.

The greatest potential source of microbial contamination in a traditional aseptic environment is people. The interaction of people and process is also not consistent. One way to significantly minimize this potential microbial exposure and variability is to separate the people from the process. Newer aseptic installations and upgrades are introducing barrier technology. This technology maintains the environmental conditions around the product at Class 100 or better while allowing personnel access only by way of glove ports. Consequently there is no direct interaction of people and process. This approach greatly enhances the potential for sterility assurance—from about 10^{-3} to 10^{-5} or 10^{-6} . One problem continues to be how to demonstrate this high level of sterility assurance. Although media fills could be used, it would be very expensive to perform fills with 100,000 or more units. Alternative approaches involving microbial evaluation of the air and the application of mathematical models are being considered.

Another benefit from the use of barrier technology is that the high-quality (expensive) air needs to be supplied only to the product operational area and not to the entire room.

VALIDATION OF ETHYLENE OXIDE STERILIZATION

This process is used for the sterilization of components but *not* for products. Because of the inherent health hazards associated with the use of ethylene oxide,

its use is tending to diminish. Key parameters to be included in the validation study include:

1. Distribution of temperature, ethylene oxide and humidity in the sterilization chamber.
2. Penetration of gas and moisture of the material to be sterilized.
3. Lethality calculations based on kill of known numbers of resistant bacteria or spores.
4. Removal of ethylene oxide and ethylene glycol residues.

VALIDATION OF RADIATION STERILIZATION

Gamma radiation using cobalt-60 is used for the sanitization and sterilization of many pharmaceutical raw materials and products. Usually these are solids or nonaqueous preparations because water when irradiated generates free radicals, which tend to cause degradation. Gamma radiation is easy to use since time is the only variable once dosage has been established. There is also some evidence that gamma irradiation can reduce endotoxin levels.

The validation of a gamma irradiation sterilization process involves three stages:

1. Product qualification evaluates the impact of radiation on the product. Three levels of radiation may be determined: (i) Maximum Tolerated Level—the highest dose that fails to induce an unacceptable change in the product. (ii) Maximum Process Dose—based on the defined sterilizing dose to be applied and the highest level of exposure in any unit of product. (iii) Minimum Process Dose—the opposite of (ii). The optimum situation is for Maximum and Minimum Process values to be close but significantly lower than the Maximum Tolerated Level.

Assessment of impact must use real-time stability studies, since accelerated conditions may result in more rapid degeneration of free radicals and give an impression of greater stability.

2. Equipment qualification is normally performed by the operator of the facility and should address design, installation, operation, and maintenance.
3. Process qualification should include:
 - (a) Sterilization approach, of which there are three: (i) overkill, which usually involves radiation doses in excess of 25 kGy and can only be used for products that are radiation stable; (ii) bioburden, which relies on a lower level of radiation based on the known and constant bioburden of the product; and (iii) species-specific, which uses an even lower radiation dosage and is particularly

useful for products with a low, nonresistant bioburden such as pharmaceuticals.

- (b) Dose distribution in the loads using well-defined loading patterns.
- (c) Biological challenge using *B. pumilis*.
- (d) Cycle interruption studies.

§211.115 REPROCESSING

(a) Written procedures shall be established and followed prescribing a system for reprocessing batches that do not conform to standards or specifications and the steps to be taken to insure that the reprocessed batches will conform with all established standards, specifications, and characteristics.

(b) Reprocessing shall not be performed without the review and approval of the quality control unit.

The failure of a batch of product to meet the quality standards must be viewed as a failure of the quality control process. The main causes of failure include:

- 1. Malfunction of equipment or services.
- 2. Noncompliance with defined procedures by operating personnel.
- 3. Atypical behavior of materials that comply with their specifications.

If none of these causes can be demonstrated, it is possible that the process had been inadequately validated and that one or more of the operating parameters are actually outside of acceptable limits. In such circumstances revalidation may be required before further lots are processed.

In addition to approving a reprocessing process, quality control should also carefully review what testing and evaluation is to be performed on the reprocessed batch. Release specifications are usually designed to evaluate a batch produced under normal circumstances and may be inadequate for reprocessed batches. Consequently it is essential that the evaluation of reprocessed batches is approved by quality management. Factors to be considered would include:

- 1. Whether any specification tests are not performed routinely, reliance being placed on validation data. Examples of this could include dissolution performed only at the uncoated stage of a film coated tablet—recoating may affect this—or content uniformity.
- 2. Whether the reprocessing might have affected product stability and its shelf life. This could happen for a liquid product requiring a reheat stage to fully dissolve some raw materials.

The practice of adding a small amount, say 10%, of the rejected batch to subsequent lots of product, based solely on the assumption that most tolerances are $\pm 10\%$, is nonvalid. First, there is no evidence to indicate that the rejected processed material will not change the characteristics beyond the specifications. Second, and more important, Current Good Manufacturing Practices require that the manufacturer try to attain the product specifications; tolerances are established to take into account only unavoidable processing variation and the accuracy and reproducibility of test methods. It is not good practice to permit a lowering of target standards by adding material whose effect on the process is not known but is assumed to lower the desired quality target, even though the quality remains within specifications. If reprocessing by addition to subsequent batches is practiced, it is necessary to confirm that this does not adversely affect the target values for product quality.

EXAMPLES OF OBSERVATIONS FROM FDA 483 CITATIONS

1. Annual revalidation of the sterility test room was not performed as required by the firm's procedures.
2. The master formula does not state a time limit for holding filtered bulk drug compound prior to filling and terminal sterilization.
3. Lack of validation of the manufacturing of the various coating solutions such as gelatin solution, sub coating powder, and syrup solution.
4. Batch manufacturing instructions do not provide sufficient written detail to ensure the uniformity of the production process from batch to batch.
5. There is no final summary by management to verify that the validation data has been reviewed, that all requirements of the protocols have been met, and that the systems are considered validated.
6. The validation program for drug products is incomplete and fails to provide for physical specifications for drug substance, sampling approximately the equivalent weight of a dosage unit to demonstrate blend uniformity, in-process individual weight variation, comparison of dissolution and granulation studies between biobatches and production batches.
7. The SOP for validation or revalidation does not require that specifications and acceptance criteria be determined prior to validation.
8. There were no SOPs for the QA investigations of product failures, laboratory failure investigations, and stability investigations.
9. Validation is inadequate in that it does not include tablet thickness, hardness, weight, or dimensions.

10. There is no established time limit for sterile filling operations.
11. The firm lacks access to the source code for software.
12. Start/stop times are not routinely recorded on the batch production records (for sterile products).
13. Filter validation does not include testing of parenteral products for extractables.
14. Of the thirty-one validation studies conducted all are invalid for one or more of the following reasons: (a) lots chosen for prospective study are nonsequential, (b) lots initially identified as validation batches are eliminated from the study for various reasons, (c) study protocols do not identify critical process control points, (d) raw material and inprocess specifications such as particle size distribution, pour bulk density, tap bulk density, moisture, etc. have not been established prior to validation.

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Following study of this chapter, it might be helpful for staff review, to discuss specific guides provided by the FDA to their field staff and others, that are pertinent as Regulatory Action Guidance.

Sec. 460.800 Parametric Release—Terminally Heat Sterilized Drug Products (CPG 7132a.13)

BACKGROUND:

In 1985, FDA approved supplemental new drug applications for certain large volume parenteral drug products, which substituted parametric release for routine lot by lot end-product sterility testing.

Parametric release is defined as a sterility release procedure based upon effective control, monitoring, and documentation of a validated sterilization process cycle in lieu of release based upon end-product sterility testing (21 CFR 211.167). All parameters within the procedure must be met before the lot is released.

POLICY:

This policy applies only to parenteral drug products which are terminally heat sterilized. It does not apply to products sterilized by filtration or ethylene oxide. This policy does not preempt requirements of Section 505 of the FD&C Act. Approved supplements providing for parametric release are required for holders of new drug applications. (21 CFR 314.70(b))

Parametric release, in lieu of end product sterility testing, is acceptable when all of the following parameters are met and documented.

1. The sterilization process cycle has been validated to achieve microbial bioburden reduction to 10^9 with a minimum safety factor of an additional six loga-

rhythm reduction. Cycle validation includes sterilizer heat distribution studies, heat distribution studies for each load configuration, heat penetration studies of the product, bioburden studies, and a lethality study referencing a test organism of known resistance to the sterilization process. All cycle parameters must be identified by the manufacturer as critical (e.g., time, temperature, pressure) or non-critical (e.g., cooling time, heat-up time). Under parametric release, failure of more than one critical parameter must result in automatic rejection of the sterilizer load (see paragraph D concerning biological indicators). (21 CFR 211.113 (b))

2. Integrity for each container/closure system has been validated to prevent in-process and post-process contamination over the product's intended shelf-life. Validation should include chemical or microbial ingress tests utilizing units from typical products. (21 CFR 211.94)
3. Bioburden testing (covering total aerobic and total spore counts) is conducted on each batch of presterilized drug product. Resistance of any spore-forming organism found must be compared to that of the organism used to validate the sterilization cycle. The batch is deemed non-sterile if the bioburden organism is more resistant than the one used in validation. (21 CFR 211.110)
4. Chemical or biological indicators are included in each truck, tray, or pallet of each sterilizer load. For chemical indicators, time/temperature response characteristics and stability are documented and for each sterilization cycle minimum degradation values are established. Chemical indicators cannot be used to evaluate cycle lethality.

Documentation is required for biological indicators (BIs). Documentation for each BI lot shall include an organism's name, source and D-value, spore concentration per carrier, expiration date, and storage conditions. BIs can be used to evaluate cycle lethality where equipment malfunction prevents measurement of one critical cycle parameter. If more than one critical parameter is not met, the batch is considered non-sterile despite BI sterility. (21 CFR 231.165(e) and 211.167)

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SUB CHAPTER 490 VALIDATION

Sec. 490.100 Process Validation Requirements for Drug Products Subject to Pre-Market Approval (CPG 7132c.08)

BACKGROUND:

Validation of manufacturing processes is a requirement of the current good manufacturing practice (CGMP) regulations for finished pharmaceuticals (21 CFR Part 211). Validation is based on the documented successful evaluation of multiple full scale batches (usually at least three (3)) to provide assurance that the processes will reliably meet predetermined

specifications. Refer to the Guideline of General Principles of Process Validation (May 1987) (distributed by the Center for Drug Evaluation and Research (CDER)) for further details.

The pre-approval inspection compliance program (7346.832) also emphasizes the importance of process validation to ensure the safety, efficacy, and quality of drug products. Although the program does not require completion of multiple batch process validation before an application may be approved, completion of such process validation is a CGMP requirement that must be met before any shipments of the products are made.

In addition, for products intended to be sterile, applicants are required to submit data to the applications that demonstrate the effectiveness of the intended sterilization or aseptic processing procedures. The center evaluates the data as part of the application approval process. Such data may be derived prior to undertaking full-scale production. For example, the data may be obtained by conducting media fills to determine the effectiveness of the aseptic processing procedures or by running simulated product along with biological indicators through autoclave cycles to determine the effectiveness of steam sterilization procedures.

Applications for sterile and non-sterile drug products may be approved by a center prior to the firm's completion of full-scale process validation.

The purpose of the pre-approval inspection is to audit the completeness and accuracy of the submitted data. The inspection also evaluates the effectiveness of important CGMP facilities and systems that bear on sterility assurance including, but not limited to: High Efficiency Particulate Air (HEPA), Heating Ventilation Air Conditioning (HVAC), facility conditions, and water systems.

POLICY:

1. During the pre-approval inspection, any process validation data that is available should be evaluated and any process validation deficiencies reported to the firm. Based on the lack of completed process validation data, the district should monitor the firm's post-approval validation efforts, and initiate regulatory action where product has been shipped and there are deficiencies with validation that would support such action. Seizure should be considered when there are supportable deficiencies with validation or the evidence demonstrates the product does not comply with specifications. Recommendations for enforcement action due to non-compliance with the CGMP regulations should cite 501(a)(2)(B) of the Act, 21 U.S.C. 351(a)(2)(B) based on violation of 21 CFR 211.100.

The district should recommend withholding approval of an application if any completed validation efforts include data of questionable validity or demonstrate that the process is not valid and the firm has not committed to making appropriate changes.

2. Rarely, the completion of multiple batch process validation prior to product shipment may be impractical due to public health considerations. For example, the public health benefits of expediting availability of clinically important drugs with a very limited market (e.g., certain orphan drug products) may outweigh

the need to await completion of full multiple batch process validation. Under such circumstances, the firm is expected to:

- A. Document the reason that complete process validation is impractical prior to shipment of the product.
- B. Establish and commit to following an adequate protocol to complete the validation of the manufacturing process. In this regard, successful validation of each batch of the multiple batch validation study must be completed prior to shipment of the batch.
- C. Establish and follow more extensive testing and process controls to ensure batch uniformity and conformance with predetermined specifications.

The district should consult with the center before initiating regulatory action under these circumstances.

- 3. Process validation requirements for bulk pharmaceutical chemicals (BPC) differ somewhat from those required for dosage form products. Refer to the BPC Inspection Guide (CDER revised, September 1991) for details. Based on recent emphasis by FDA, the industry has begun to formally validate the manufacturing processes for BPCs. The district should recommend withholding approval of an application based on the lack of process validation for the BPC where:
 - A. The firm has not established or is not following an adequate plan to validate all BPCs; or,
 - B. The process is not valid, as demonstrated by repeated batch failures due to manufacturing process variability not attributable to equipment malfunction or operator error.

NOTE: This compliance policy guide (CPG) also applies to pre-market approval applications submitted to the Center for Veterinary Medicine (NADAs or ANADAs). The CPG reference may be found at 7125.38 (See Sec. 638.100).

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SUB CHAPTER 420 COMPENDIAL/TEST REQUIREMENTS

Sec. 420.100 Adulteration of Drugs Under Section 501(b) and 501(c) of the Act. * Direct Reference Seizure Authority for Adulterated Drugs Under Section 501(b) * (CPG 7132a.03)

BACKGROUND:

Section 501(b) of the Food, Drug, and Cosmetic Act (the Act) deems an official drug (i.e., a drug purported to be or represented as a drug the name of which is recognized in an official compendium) to be adulterated if it fails to conform to compendial standards of quality, strength or purity. Compendial tests or assay methods are used when determining such conformance under 501(b); the standards are stated in individual monographs as well

as portions of the General Notices section of the USP/NF. Standards and test methods have been established for such characteristics as potency, sterility, * dissolution *, weight variation and content uniformity.

If an official drug fails to conform to one or more compendial standards of strength, quality or purity, but plainly states on the label how it differs from the standard, then the drug is not deemed to be adulterated under Section 501(b).

Section 501(c) of the Act deems * a drug that is not recognized in an official compendium to be adulterated if it fails to meet the strength, purity or quality which it purports or is represented to possess. The applicable quality standards for a drug not recognized in an official compendium can be determined from such sources as the labeling of the drug (or drug product), the manufacturer's written specifications, and new drug applications. (Test methods are usually contained in the written specifications or new drug application). *

POLICY:

Any official drug which, when tested by compendial methods, fails to conform to compendial standards for quality, strength, or purity, is adulterated unless the differences from such standards are plainly stated on the drug's label.

Any * drug which is not recognized in an official compendium is adulterated if its strength differs from, or its purity or quality falls below that which it purports or is represented to possess, when tested by scientifically sound methods. *

REGULATORY ACTION GUIDANCE:

Recommendations for regulatory action will be considered in the above instances of adulteration. The regulatory action of choice will depend upon the circumstances of each case.

In cases where there is a health hazard, the first choice of action should be recall, particularly for drugs found to be non-sterile, and for narrow therapeutic range drugs that fail potency or dissolution tests. However, where the district office has advised the firm of such a defective product, and the firm fails to recall, seizure should be considered. Seizure recommendations charging adulteration under section 501(c) should be submitted to the Office of Compliance, Center for Drug Evaluation and Research (HFD-300) (CDER).

District offices are authorized to submit seizure recommendations, charging adulteration under section 501(b), directly to the Office of Enforcement without CDER review under the following circumstances, provided introduction or delivery for introduction into interstate commerce has been documented:

1. An official sample of either a compendial bulk pharmaceutical chemical or a compendial finished dosage form has been analyzed using the compendial methods without modification and found to fail both the original and check analyses.
2. The analyzing laboratory has certified in the transmittal memorandum that an unmodified compendial method was used.

Note: No tolerance need be applied beyond that provided by the official compendium.

3. For sterile products, no check analysis is needed provided the compendial sterility test was utilized without modification, the product is one that is required to be sterile, and all relevant laboratory controls (including positive and negative) are satisfactory.

Where the analyzing laboratory deviates from the official compendial analytical method(s), a detailed description of the deviation(s) and justification for such deviation(s) can be submitted to CDER for review. In such cases, CDER will review only the deviation(s) and not the choice of regulatory action or other documentation.

For seizure actions, the charges may be drafted as follows:

That the article of drug was adulterated, when introduced into and while in interstate commerce and is adulterated while held for sale after shipment in interstate commerce within the meaning of 21 U.S.C. 351(b), in that it purports to be and is represented as a drug, the name of which is recognized in an official compendium. (United States Pharmacopeia) and its strength differs from, and its quality and purity falls below the standard set forth in such compendium because it fails the official (INSERT TYPE OF TEST) test.

or

That the article of drug was adulterated, when introduced into and while in interstate commerce and is adulterated while held for sale after shipment in interstate commerce within the meaning of 21 U.S.C. 351(c), in that it is a drug not subject to the provisions of 21 U.S.C. 351(b) and its strength differs from, and its purity and quality falls below that which it purports or is represented to possess because (e.g., the drug contains less than the amount of (INSERT NAME OF INGREDIENT) on the label).

It should be kept in mind that the types of adulteration found under 501(b) and 501(c) may be indicative of a wider problem involving failure of the manufacturer to adhere to current good manufacturing practice that should be addressed.

Issued: 10/1/80

Revised: 5/1/92

Sec. 420.200 Compendium Revisions and Deletions (CPG 7132.02)

BACKGROUND:

The USP and NF are continually being revised to keep pace with advances in new drugs, analytical methods, changes in governmental regulations, etc. The revisions are put into effect through periodic publication of supplements and publication of new editions of the compendia every five years. The revisions may, among other things, add monographs for

new drugs, delete monographs for others, change analytical procedures, or alter specific requirements affecting strength, quality, and purity of the article. The official article may be a drug product, an active ingredient, or a pharmaceutical necessity.

On 7/1/80, when the combined USP XX/NF XV became official, a major change occurred. All monographs for dosage forms and active ingredients were placed in the USP whereas all monographs for pharmaceutical necessities were placed in the NF. It is anticipated that because of these changes that many more articles, transferred from one compendium to the other, will have to be relabeled than would normally be expected when a new compendium becomes official. However, our basic policy will remain unchanged.

POLICY:

1. Articles shipped prior to and after the official date of the current USP or NF.
 - A. All official articles shipped after the current USP/NF became official should be in compliance with the current compendia.
 - B. All official articles shipped prior to the date that the current USP/NF became official should be in compliance with the official compendia in effect at the time of shipment.
2. Articles that have been dropped from the USP or NF.

Articles which at one time or another were recognized in either the USP or NF, but are no longer recognized in the current edition of either compendium should, if they are labeled as conforming to a superseded USP or NF, bear a statement that the article is no longer official.

3. Articles that differ in strength, quality, or purity from the current USP or NF.

Under Section 501(b) of the Act, a drug defined in an official compendium shall not be without the approval of a supplement under the conditions described in that section. Such changes included:

1. A change to more stringent specifications without altering the method described in the approved application.
2. Inclusion of additional specifications and methods without deletion of those described in the approved application.
3. The alteration of specifications or methods for inactive ingredients to bring them into compliance with new or revised specification or methods in an official compendium.

Issued: 10/1/80

Sec. 420.400 Performance of Tests for Compendial Requirements on Compendial Products (CPG 7132.05)

BACKGROUND:

There have been inquiries from the field and industry concerning the following four items as they apply to the manufacture of compendial (USP/NF) drug products.

1. Does a firm have to use the compendial methodology on a batch release basis, to determine whether its product meets the requirements of the monograph?
2. Does the word “specifications” as used in 21 CFR 211.165 refer to compendial specifications or those set up by the firm’s quality control unit?
3. Does a firm have to test for all requirements listed in the monograph for a compendial product?
4. Are the compendial testing requirements the same for products destined for the commercial market and the military?

POLICY:

1. Compendial methods need only be applied, as a batch release test, where a firm has made specific commitments to do so (as in a new drug application), or where the official method is the only appropriate test. It should be noted that neither the USP/NF nor the CGMP regulations necessarily require a firm to utilize, as a batch release test, the methods and procedures stated in the official compendia.

What is required is that official drug products conform to the appropriate compendial standards. This conformance must be assured by suitable means, including adequate manufacturing process validation and control. Scientifically sound alternative test methods may be acceptable for the purpose of batch release testing. However, in the event of a dispute as to whether or not a drug product meets the standard, the compendial method will be applied as the referee test.

2. The term “specifications” as used in 21 CFR 211.165 refers to the criteria established by manufacturers to assure that their products have the properties they purport to possess. Typically, these specifications are identical to, or more stringent than those contained in the compendia themselves. However, the manufacturer’s specifications for standards of strength, quality and purity may be less stringent in those cases in which the differences from the official standards are stated on the product label; such alternate standards must not adversely affect the product’s safety or efficacy.
3. Where an official product purports to conform to the standards of the USP/NF the manufacturer must assure that each batch conforms to each monograph requirement. This assurance must be achieved by appropriate means, including process validation and controls and end product testing. However, the nature and extent of end product testing which is needed will depend upon the circumstances. Factors to consider in determining the need to test each batch for a given monograph requirement include: the adequacy of the manufacturer’s process validation, adequacy of in-process manufacturing controls, and the nature of the particular product characteristic which is the subject of the specification (e.g., potency, sterility, content uniformity). Therefore, in some cases it may not be necessary for a manufacturer to test each batch for each monograph requirement.
4. Compendial testing requirements are the same for products destined for commercial and military use unless the Defense Personnel Support Center (DPSC) insists upon certain requirements as part of military contracts. For example,

DPSC can insist that only compendial methods be used and that each batch be tested for every monograph specification, whereas, as explained above, FDA considers that alternative procedures may sometimes be acceptable. Under the Government Wide Quality Assurance Program FDA must assure that the drug manufacturer abides by the terms of the military contract, including testing requirements.

Issued: 10/1/80

Sec. 420.500 Interference with Compendial Tests (CPG 7132a.01)

BACKGROUND:

The recurring question is: What is the legal status of a compendial drug in which an added substance interferes with the compendial assay of the product, even though the product may be fully potent as shown by other methods of analysis?

Section 501(b) of the Federal Food, Drug, and Cosmetic Act states that a drug is deemed to be adulterated if it is recognized in an official compendium and its strength differs from, or its quality or purity falls below the standards set forth in the compendium. Determination as to strength, quality, or purity shall be made in accordance with tests or methods of assay set forth in such compendium.

The USP XX in the section on Added Substances (p. 4) states that suitable substances such as bases, carriers, coatings, colors, flavors, preservatives, stabilizers, vehicles may be added to a pharmacopeial dosage form to enhance its stability, usefulness, or elegance, or to facilitate its preparation. The USP restrictions on the use of such added substances include "if they do not interfere with the assays and tests prescribed for determining compliance with the pharmacopeial standards."

POLICY:

A compendial drug product containing an added substance which interferes with the compendial assay of the product would be adulterated under 501(b) of the Act.

Issued: 10/1/80

SUB CHAPTER 425 COMPUTERIZED DRUG PROCESSING

Sec. 425.100 Computerized Drug Processing; CGMP Applicability to Hardware and Software * (CPG 7132a.11)

BACKGROUND:

The use of computers in the production and control of drug products is quickly increasing. Questions have been raised as to the applicability of various sections of the Current Good

Manufacturing Practice Regulations to the physical devices (hardware) which constitute the computer systems and to the instructions (software) which make them function.

POLICY:

Where a computer system is performing a function covered by the CGMP regulations then, in general, hardware will be regarded as equipment and applications software¹ will be regarded as records. The kind of record (e.g., standard operating procedure, master production record) that the software constitutes and the kind of equipment (e.g., process controller, laboratory instrument) that the hardware constitutes will be governed by how the hardware and software are used in the manufacture, processing, packing, or holding of the drug product. Their exact use will then be used to determine and apply the appropriate sections of the regulations that address equipment and records.

¹ Applications software consists of programs written to specified user requirements for the purpose of performing a designated task such as process control, laboratory analyses, and acquisition/processing/storage of information required by the CGMP regulations.

* Material between asterisks is new or revised *

Issued: 10/19/84

Revised: 9/4/87

Sec. 425.200 Computerized Drug Processing; Vendor Responsibility (CPG 7132a.12)

BACKGROUND:

Computer systems used in the production and control of drug products can consists of various devices (hardware) and programs (software) supplied by different vendors, or in some cases by a single vendor. It is important that such computer systems perform accurately and reliably, * and * that they are suitable for their intended use.

Questions have arisen as to the vendor's responsibility in assuring computer systems performance and suitability. When an integrated system, composed of elements from several different vendors, fails, it can be especially difficult to attribute the cause of a problem to one particular vendor.

POLICY:

The end user is responsible for the suitability of computer systems (hardware and software) used in manufacture, processing or holding of a drug product.

* The vendor may also be liable, under the FD&C Act, for causing the introduction of adulterated or misbranded drug products into interstate commerce, where the causative factors for the violation are attributable to intrinsic defects in the vendor's hardware and

software. In addition vendors may incur liability for validation, as well as hardware/software maintenance performed on behalf of users. *

* Material between asterisks is new or revised *

Issued: 1/18/85

Revised: 9/4/87

Sec. 425.300 Computerized Drug Processing; Source Code for Process Control Application Programs (CPG 7132a.15)

BACKGROUND:

An increasing number of pharmaceuticals are being manufactured under the control of computer systems. The manufacturing procedures, control, instructions, specifications and precautions to be followed within such automated systems are embodied in the computer program(s) which drive the computer. Depending of the complexity of the programs, they may also contain controlling data on product formulation, batch size, yields and automated in-process sampling/testing procedures. In a manual system such procedures, instructions, specifications, precautions and other controlling data would be embodied in master production records which must be reviewed and approved before implementation and which must be maintained, as required by the current good manufacturing practice regulations (CGMP's). Such manual records are, of course, prepared in human readable form.

In the case of computerized drug process control, certain information required by CGMP's to be in a master production record is contained in the source code for the application program. (An application program is software written to specified user requirements for the purpose of performing a designated task.) Source code is the human readable form of the program, written in its original (source) programming language. Source code must be compiled, assembled, or interpreted before it can be executed by a computer. Because the source code ultimately has a direct and significant bearing on drug product quality as manual master records, it is vital that source code and supporting documentation be reviewed and approved by the drug manufacturer prior to implementation, and be maintained as the CGMP's require for master production and control records. (E.g., see 21 CFR 211.100, 211.180, and 211.186.) Careful review of source code and its documentation is especially important for assuring that process specifications, conditions, sequencing, decision criteria, and formulas have been properly incorporated into the computer program; source code should also be reviewed to detect and remove dead code—non-executable instructions which are usually artifacts of earlier versions of the program.

Supportive program documentation, such as flow diagrams and explanatory narratives, can be useful in understanding and reviewing source code. However, such documentation is not an acceptable substitute for source code itself.

We regard source code and its supporting documentation for application programs used in drug process control to be part of master production and control records, within the meaning of 21 CFR Parts 210 and 211.

Accordingly, those sections of the current good manufacturing practice regulations which pertain to master production and control records will be applied to source code.

Sec. 460.600 Content Uniformity Testing of Tablets and Capsules (CPG 7132a.14)

BACKGROUND: Refer to 21 CFR 211.167 Special Requirements.

There has been some misunderstanding surrounding the applicability of content uniformity testing requirements to tablets and capsules, particularly for non-official products, i.e., those not recognized as official in the United States Pharmacopeia (USP). Added to this is the confusion created by recent changes in the USP test requirements for official products. In addition to the existing standard for the individual dosage unit assay, the USP included a specification for relative standard deviation to limit large variations in test results. However, many firms have been reluctant to incorporate the relative standard deviation specification into their standard operating procedures.

POLICY:

The following policy is applicable to tablet or capsule dosage forms.

1. Official Products

Any drug product recognized in the USP must comply with the USP requirement for content uniformity if such requirement is included in the monograph for the drug. The product must comply with the specifications for individual dosage unit assay and for relative standard deviation. Both requirements are applicable regardless of whether or not the product in question is subject to a new drug application (NDA). If an approved NDA does not currently provide for complete content uniformity testing, or provides specifications that are inconsistent with the USP monograph, the NDA holder must submit a change to provide for such testing, pursuant to 21 CFR 314.70(d)(1).

2. Non-official Drug Products

The Food, Drug, and Cosmetic Act requires that drug products which are not official (and therefore not subject to compendia requirements) nonetheless meet standards of strength and quality which they purport or are represented to possess. Current good manufacturing practice regulations (21 CFR 211.160) require the establishment of scientifically sound and adequate specifications to assure those product attributes.

Specifications for content uniformity are required, within this context, for tablets and capsules which contain less than 50 mg of any active ingredient. Requirements for content uniformity include individual dosage unit assays and establishment of specifications for relative standard deviation.

Any non-official tablet or capsule dosage form which contains less than 50 mg of any active ingredient and such ingredient(s) has not been tested for content uniformity is in violation of Section 501(a)(2)(B) of the Act. In evaluating the appropriateness of test

specifications for a non-official product, it must be emphasized that although USP specifications are acceptable, and may be adopted by a firm, they are not specifically required. Scientifically sound alternative specifications may be used.

Sec. 460.700 Controlled Release Dosage Form Drugs— Rate of Release of Active Ingredients (CPG 7132a.02)

Many drugs are now offered in dosage forms that are designed to release the active ingredient(s) over a prolonged period. There is a possibility of unsafe overdosage if such products are improperly made and the active ingredients are released at one time or over too short a time interval.

Under 21 CFR 200.31 any such dosage form that contains per dosage unit (for example, capsule or tablet), a quantity of active drug ingredient which is not generally recognized as safe for administration as a single dose under the conditions suggested in its labeling, is regarded as a new drug within the meaning of Section 201(p) of the Act.

Formerly regulatory action was considered only when an NDA existed and the product failed the NDA method of analysis for the rate-of-release. However, since the revised GMPs for finished pharmaceuticals became effective on 3/1/79 we are prepared to consider regulatory action for non-NDA controlled release drugs where the rate-of-release, when tested by the manufacturer's own method, fails to meet the written specifications.

The following represents criteria for recommending legal action to the * Office of Compliance HFD-300 *:

1. The product has an NDA and fails to meet the NDA specifications for rate-of-release when tested by the NDA method of analysis (or a manufacturer's own specifications if they are more strict)
2. The product does not have an NDA and fails to meet the firm's specifications for rate-of-release when tested by its own method of analysis.

8

Packaging and Labeling Control (Subpart G)

§211.122 MATERIALS EXAMINATION AND USAGE CRITERIA

(a) There shall be written procedures describing in sufficient detail the receipt, identification, storage, handling, sampling, examination, and/or testing of labeling and packaging materials; such written procedures shall be followed. Labeling and packaging materials shall be representatively sampled, and examined or tested upon receipt and before use in packaging or labeling of a drug product.

(b) Any labeling or packaging materials meeting appropriate written specifications may be approved and released for use. Any labeling or packaging materials that do not meet such specifications shall be rejected to prevent their use in operations for which they are unsuitable.

(c) Records shall be maintained for each shipment received of each different labeling and packaging material indicating receipt, examination or testing, and whether accepted or rejected.

The terms labeling and packaging in the context of this section specifically exclude containers and closures, which are covered in Subpart E; advertising and promotional material are not subject to GMP regulation. However, unlabeled packaging such as corrugated shippers and dividers are to be included, although the evaluation and control may not need to be so extensive.

Labels and labeling errors have been the most frequent reason for product recall in recent years. The effective control of printed labeling (labels, inserts, cartons, foil) commences well before materials are ordered; it starts at the design and approval stage. For new or changed labeling there must be in place a procedure that clearly defines:

1. Who is to review and approve the copy. This will usually include marketing, medical, legal, regulatory affairs, production, materials management, quality assurance, and editorial.
2. What each function is to check and approve. With so many people involved, individuals may be tempted to assume that someone else has checked the various points. A typical system might include the following detailed responsibilities:
 - a. Materials management—evaluate inventory situation, identify an implementation date that will comply with regulatory or company requirements while minimizing stock write-offs or production interruptions. Identify which countries take this product so that Regulatory Affairs can evaluate any regulatory requirements and potential impacts, including potential delays in implementation.
 - b. Production—confirmation that equipment is available, or will be to introduce the change; adequate space for batch coding and expiry dating.
 - c. Marketing (or other function)—identify whether the specific change will require modification to other materials, e.g., changes to a label may require changes to inserts and cartons—identify whether other pack sizes may need to incorporate the same or equivalent change.
 - d. Medical—confirmation that any medical claims, warnings, dosage are correct.
 - e. Legal & Regulatory Affairs—confirmation that the changes meet all legal and regulatory requirements in all countries that sell the product.
 - f. Technical Service & Quality Control—identify any stability issues (primary pack changes).
 - g. Editorial—to confirm grammatical correctness and absence of typographic and print errors or omissions.
 - h. System Manager—to confirm that all appropriate approvals have been given and in the event of queries to recirculate through the system if necessary.
3. Whether the change is mandatory or voluntary and the date of introduction. For voluntary changes this is likely to relate to depletion of inventories of existing labeling.

4. Whether the labeling in question is interrelated with any other labeling and to note any impact. For example, a change to the dosage requirements on a label will almost certainly require amendment to inserts and cartons.
5. The reviewers and approvers (item 1) should preferably be defined by name. Since the approval process is so important, it is essential that approvers have undergone adequate training in the system. Additional individuals should not be allowed to authorize new labeling or changes without having undergone this training.
6. The feedback loop that confirms that the change has actually been introduced.
7. A unique numbering system that clearly distinguishes between labeling for different products and strengths and also between different versions of the same labeling.
8. Ownership of the procedure. As with any system or procedure but especially one that involves so many people, there should be designated responsibility for operation and monitoring of the system itself. This individual should routinely identify any potential weaknesses in the operation of the system and have them corrected.

The extent of the sampling and evaluation required by the regulations can be varied to match the importance of the material and the capabilities of the supplier. Special attention should be given to new or changed labeling, and a check against the previously approved text or artwork should be performed. As written, the regulations do not allow for the total elimination of sampling and evaluation, but the use of certified vendors will allow this to be minimal. The regulations also do not permit use of packaging and labeling materials prior to evaluation and release. This is similar to the requirement for components, but since these evaluations are usually of short duration this is unlikely to result in any practical delays.

Low levels of mix-up with labeling are difficult, if not impossible, to detect at the incoming inspection stage. This further accentuates the need to build in quality at the design and supplier stages:

1. Avoid gang printing if possible [see §211.122(f)].
2. Design to avoid look-alike labeling especially for different strengths of the same product and if possible for different products run on the same packaging line. Different colors, sizes and shapes can all help.
3. In addition to the unique numbering system include bar codes that can be used in association with on-line scanning during the labeling operation. This will be expanded upon later.
4. Use roll-feed labels wherever possible but ensure that any splicing done by the supplier is clearly marked.

5. Only use suppliers who have facilities and procedures with a high probability of achieving the required quality consistency; this will usually require a visit to the supplier. The evaluation of packaging and labeling suppliers has on occasion not received the same level of attention as the suppliers of BPCs. With the multiplicity of labels, the tendency for marketing to prefer a company image for all labeling, and the frequent changes that are implemented, the potential for errors or mix-ups is high. Consequently, supplier systems must be well designed and followed. This should include a procedure to destroy obsolete plates or other masters before commencing work on a new version. One effective way is to have the obsolete masters returned to the customer (pharmaceutical manufacturer).

The requirement in §211.122(b) to reject materials that do not meet specification seems both obvious and at the same time controversial. For example, must a label whose color is marginally outside of the specification be rejected? In such instances the problem appears to be semantic. If color ranges are not considered critical with respect to product quality then ranges should perhaps be expressed as “action levels” with reference to who must be consulted when material is received outside of the range. Too much variability could have quality implications—colors might overlap with those of other products, causing consumer confusion, consumer perception of quality could be affected on receiving such variability, and also this might indicate that the supplier has less control over the printing process than is required.

Records must be retained to indicate the evaluation results and disposition of each delivery of material. The data in these records should also be used to monitor supplier performance and to detect adverse trends which may require attention.

- (d) Labels and other labeling materials for each different drug product, strength, dosage form, or quantity of contents shall be stored separately with suitable identification. Access to the storage shall be limited to authorized personnel.
- (e) Obsolete and outdated labels, labeling, and other packaging materials shall be destroyed.

Storage of labeling must be done in a manner that will minimize the potential for mix-ups or unapproved release to production. Materials for different products and for different strengths of the same product are to be kept separate—often by the use of drawers, cubicles, or cupboards. When label changes are being phased into production, the current and new versions should be kept apart. Obsolete labeling should immediately be moved to a “nonactive” location, usually a reject area, pending destruction.

Labeling storage is usually a part of the warehouse and should have restricted access. Unless the overall warehouse is operated as a secure area, the space allocated to labeling will need separate segregation. Labeling must be adequately protected from dirt and dust which, in addition to affecting appearance, can adversely impact on adhesion characteristics. Certain labeling components, such as foil, laminates, cellophane, and self-adhesive labels, may also require storage under defined conditions of temperature and humidity.

(f) Use of gang-printed labeling for different drug products, or different strengths or net contents of the same drug product, is prohibited unless the labeling from gang printed sheets is adequately differentiated by size, shape, or color.

(g) If cut labeling is used, packaging and labeling operations shall include one of the following special control procedures:

(1) Dedication of labeling and packaging lines to each different strength of each different drug product;

(2) Use of appropriate electronic or electromechanical equipment to conduct a 100% examination for correct labeling during or after completion of finishing operations; or

(3) Use of visual inspection to conduct a 100% examination for correct labeling during or after completion of finishing operations for hand applied labeling. Such examination shall be performed by one person and independently verified by a second person.

(h) Printing devices on, or associated with, manufacturing lines used to imprint labeling upon the drug product unit label or case shall be monitored to assure that all imprinting conforms to the print specified in the batch production record.

Gang printing consists of printing different labeling on the same sheet and then cutting and separating the different labeling. This technique has a high potential for mix-up during the cutting and separating stages, and most pharmaceutical companies now avoid this approach. The regulations prior to 1994 acknowledged the risks but did allow gang printing provided certain safeguards were employed during the cutting and separating stages. The update prohibits gang printing unless the individual items are sufficiently different.

Subsection (g) was also revised to address the broader issue of cut labeling. While the risks at the printer are significantly less than for gang printing, the potential for mix-ups there and subsequently is still high. This is accentuated if excess labeling is returned to stock. The regulations now require additional checking, preferably by electronic or other automated means, although visual confirmation is allowed for hand labeling operations. This update created problems for much of the industry since the initial draft FDA proposal had referred only to labels and not to labeling. Consequently, companies were moving toward compliance with respect to labels (the primary container label). When the final rule,

effective August 3, 1994, was published, industry asked for relief with respect to other labeling to allow time to evaluate, obtain, install and validate equipment. A stay until August 1996 was allowed for other labeling.

Some pharmaceutical operations include in-house printing of components either on-line or off-line. Examples of this include ceramic or silk-screen printing of ampoules and silk-screen printing of tubes and plastic bottles. In these cases the printing operations should be set up, operated and monitored in a manner equivalent to that of a supplier. Printing screens, when used, should be carefully examined for conformity to approved text, correct layout, absence of tears and holes, and absence of blocked holes or letters.

§211.125 LABELING ISSUANCE

- (a) Strict control shall be exercised over labeling issued for use in drug product labeling operations.
- (b) labeling materials issued for a batch shall be carefully examined for identity and conformity to the labeling specified in the master or batch production records.
- (f) Procedures shall be written describing in sufficient detail the control procedures employed for the issuance of labeling; such written procedures shall be followed.

These three subsections relate to the procedures for storage and issue of labeling. Labeling materials should be supplied against a written order that relates to a specific packaging operation. The batch documentation should define the number of units to be issued and will normally include a small overage to allow for normal line set up and wastage. Labeling materials should be delivered to the packaging line in a secure manner to assure no potential for loss or mix-up between issue and use. Prior to acceptance onto the line, the supervisor should confirm the absence of any labeling associated with the previous packaging run and also confirm that the correct labels, and number, have been provided [see also §211.130(c)(d)].

- (c) Procedures shall be utilized to reconcile the quantities of labeling issued, used, and returned, and shall require evaluation of discrepancies found between the quantity of drug product finished and the quantity of labeling issued when such discrepancies are outside narrow preset limits based on historical operating data. Such discrepancies shall be investigated in accordance with §211.192. Labeling reconciliation is waived for cut or roll labeling if a 100% examination for correct labeling is performed in accordance with §211.122(g)(2).
- (d) All excess labeling bearing lot or control numbers shall be destroyed.

(e) Returned labeling shall be maintained and stored in a manner to prevent mix-ups and provide proper identification.

One of the more sensitive and controversial sections of the CGMP regulations was §211.125(c). In order to reconcile issue, use, and return, it is necessary to count labels on receipt from the supplier, to count and issue precise numbers for each packaging run, to count the number of units produced, to count the number of labels damaged or destroyed during the packaging run, and to count the number returned to stock or to be destroyed. This is not only a time-consuming and expensive operation; it is also prone to error. A precise count of labeling damaged or destroyed on-line is virtually impossible, and this is acknowledged by acceptance of reconciliation limits based on historic achievement. If reconciliation values fall outside of the accepted range an evaluation should be initiated. This usually will include more detailed examination of the batch to identify if there is any mislabeling, also rechecking of any returned labeling and of inventory records. Even the application of a relatively tight 0.5% limit would allow a discrepancy of 500 in a run of 100,000 units—which could be due to a counting error or to mislabeling.

Over the years labeling errors have continued to be a significant cause for product recalls. The changes in §211.125(c) and §211.122(g) have addressed many of the potential causes for these errors—prohibition of gang printing and more intensive and more effective reconciliation procedures. Electronic scanning of labeling either for bar codes or total scanning should be 100% effective. The emphasis by industry now needs to be focused on labeling design, approval, and printing. Recent examples of recalls, with use of on-line electronic scanning, have included

- use of an obsolete master to make a minor modification and
- omission of a controlled substance designation after a change that was missed on editorial review.

Excess labeling may be returned to stock provided it is uncoded and undamaged. Great care must be taken to ensure return to the correct storage drawer or area. There may be an advantage to note the batch for which the returned labeling had been issued so that reevaluation is easy in the event of a later query (before they are reissued).

§211.130 PACKAGING AND LABELING OPERATIONS

There shall be written procedures designed to assure that correct labels, labeling, and packaging materials are used for drug products; such written proce-

dures shall be followed. These procedures shall incorporate the following features:

(a) Prevention of mix-ups and cross-contamination by physical or spatial separation from operations on other drug products.

(b) Identification and handling of filled drug product containers that are set aside and held in unlabeled condition for future labeling operations to preclude mislabeling of individual containers, lots, or portions of lots. Identification need not be applied to each individual container but shall be sufficient to determine name, strength, quantity of contents, and lot or control number of each container.

(c) Identification of the drug product with a lot or control number that permits determination of the history of the manufacture and control of the batch.

(d) Examination of packaging and labeling materials for suitability and correctness before packaging operations, and documentation of such examination in the batch production record.

(e) Inspection of the packaging and labeling facilities immediately before use to assure that all drug products have been removed from previous operations. Inspection shall also be made to assure that packaging and labeling materials not suitable for subsequent operations have been removed. Results of inspection shall be documented in the batch production records.

Subpart F, Production and Process Controls, covers the overall manufacturing process but an equivalent section with respect to packaging does not appear to be present. Section 211.130 refers essentially to assurance of correct labeling and packaging materials; particularly, there are no comments in relation to assurance that the correct bulk product is provided, that equipment details are noted, that fill volumes or quantities are monitored, or that equipment is suitable, qualified, calibrated and clean. However, this section will attempt to describe the overall packaging process.

The master batch packaging formula will provide the basis for each packaged dosage form. It will contain the following data fields (where appropriate):

1. Drug product name, identification number and strength.
2. Names, identification number and quantities of each packaging component:
 - a. Primary container: bottle, closure and liner, foil, laminate, etc.
 - b. Label
 - c. Carton
 - d. Insert
 - e. Tamper-evident feature
 - f. Child-resistant feature
 - g. Shipper, dividers, other protective packaging
3. Complete description of the equipment to be utilized for the packaging operation.

4. Characteristics to be monitored during filling and packaging (e.g., temperature, fill, clarity, pH, specific gravity, color, cap tightness, seal integrity).
5. Sample requirements and frequency.
6. For the specific batch being packaged:
 - a. Batch number of the bulk drug product
 - b. Packaging lot or control number assigned
 - c. Quantities of packs expected and action level value
 - d. Quantities of each packaging component issued (if different from item 2)
 - e. Expiry date to be assigned
 - f. Items 6a–e are sometimes incorporated into a separate document, the “packaging order.”

The master packaging formula and the packaging order must be written and approved by the appropriate personnel, which will usually include production and QA. No changes can be made to these master documents without reapproval.

The regulations permit spatial separation of packaging lines, but the potential for mix-ups and cross-contamination may be further reduced by physical segregation:

1. A physical barrier between adjacent lines.
2. Adequate space and physical segregation to assemble bulk product and packaging components.
3. Adequate space for assembly of finished packaged stock prior to transfer to the warehouse.
4. Accumulation tables or other space to accommodate part packaged product in the event of temporary breakdown of part of the packaging line.
5. Dust extraction over bulk table hoppers.
6. Covers over open hoppers, open empty containers, and filled but uncapped containers.
7. Avoidance of running different, but similar looking, products or packs on adjacent lines.
8. Delay start-up until all packaging components are available.
9. During extended stoppages, such as lunch breaks and shift changes, ensure that all filled units are capped, especially for liquid products.

Before commencing a packaging operation it is essential to examine the entire line to confirm that it is documented as having been cleaned; that there is no visible evidence of bulk product, components or finished product from the previous packaging run; that the line board notes the correct product, batch, control number and expiry date; that the correct materials have been delivered to

the line. Results of these inspections should form part of the batch records. A useful approach, coupled with the line board, is to prominently display on the line an authorized example of the various components of the pack.

Whenever possible, coding of control number and expiry dates should take place on-line. If off-line coding is necessary, very stringent controls must be established and followed.

Subsection (b) was inserted recently and became effective on August 3, 1994. The intent was to address the practice of filling a product but delaying labeling until a future date. There are several reasons for separating these two processes, which incidentally tends to decrease efficiency. These include:

- Packaging of a batch but labeling for individual markets (with different labeling/language requirements) only when orders are received.
- Breakdown of the labeling equipment.
- Packaging of product to be shipped to another facility/country for labeling.

Obviously, the presence of unlabeled product constitutes a high potential for risk unless the packaging is unique. At one stage the FDA appeared to be moving in the direction of requiring the identification of every unit. The application of individual identification followed by on-line scanning during future labeling would certainly minimize or eliminate the risk of applying the wrong label to a package. However, it was considered unnecessary to be so specific. Companies usually label complete boxes (shippers) or shrouded pallets. The use of secured cages is also a valuable approach. Whatever procedure is used, it must be essentially fail-safe.

FDA investigators have shown little interest in packaging operations other than labeling. While labeling is possibly the most critical packaging operation, the other areas should be addressed to assure the effectiveness of the overall packaging operation. These include:

- Installation qualification of equipment.
- Operational qualification of key operations such as tablet fillers (to assure that tablets will not block the feed chutes especially of slat fillers); liquid fillers (to determine range variability within and between filling heads); weight checkers (to determine the sensitivity and assure this is adequate to detect the defined deviations such as missing tablet, missing insert, etc.); cappers (for torque variability); and on-line scanners (to confirm they will progress good units and reject foreign labeling).
- Calibration checks on monitoring equipment at least at the beginning and end of each day (or packaging run if less than a day).

- Adequate in-process controls to confirm that the line is operating satisfactorily—label checks, weight/volume checks, torque checks, child resistance and tamper checks (see also in §211.134).

This entire subject of packaging control would benefit from more comprehensive evaluation and publication of acceptable practices.

§211.132 TAMPER-RESISTANT PACKAGING REQUIREMENTS FOR OVER-THE-COUNTER (OTC) HUMAN DRUG PRODUCTS

(a) General. The Food and Drug Administration has the authority under the Federal Food, Drug, and Cosmetic Act (the act) to establish a uniform national requirement for tamper-resistant packaging of OTC drug products that will improve the security of OTC drug packaging and help assure the safety and effectiveness of OTC drug products. An OTC drug product (except a dermatological, dentifrice, insulin, or throat lozenge product) for retail sale that is not packaged in a tamper-resistant package or that is not properly labeled under this section is adulterated under section 501 of the act or misbranded under section 502 of the act, or both.

(b) Requirement for tamper-resistant package. Each manufacturer and packer who packages an OTC drug product (except a dermatological, dentifrice, insulin or throat lozenge product) for retail sale, shall package the product in a tamper-resistant package, if this product is accessible to the public while held for sale. A tamper-resistant package is one having one or more indicators or barriers to entry which, if breached or missing, can reasonably be expected to provide visible evidence to consumers that tampering has occurred. To reduce the likelihood of successful tampering and to increase the likelihood that consumers will discover if a product has been tampered with, the package is required to be distinctive by design (e.g. an aerosol product container) or by the use of one or more indicators or barriers to entry that employ an identifying characteristic. (e.g. an aerosol product container) or by the use of an identifying characteristic (e.g. a pattern, name, registered trademark, logo, or picture). For purposes of this section, the term “distinctive by design” means the packaging cannot be duplicated with commonly available materials or through commonly available processes. For purposes of this section, the term “aerosol product” means a product that depends upon the power of a liquified or compressed gas to expel the contents from the container. A tamper-resistant package may involve an immediate-container and closure system or secondary-container or carton system or any combination of systems intended to provide a visual indication of package integrity. The tamper-resistant feature shall be designed to and shall remain intact when

handled in a reasonable manner during manufacture, distribution and retail display.

(1) For two-piece, hard gelatin-capsule products subject to this requirement, a minimum of two tamper-resistant packaging features are required, unless the capsules are sealed by a tamper-resistant technology.

(2) For all other products subject to this requirement, including two-piece, hard gelatin capsules that are sealed by a tamper-resistant technology, a minimum of one tamper-resistant feature is required.

(c) Labeling. Each retail package of an OTC drug product covered by this section, except ammonia inhalant in crushable glass ampules, aerosol products as defined in paragraph (b) of this section, or containers of compressed medical oxygen, is required to bear a statement that is prominently placed so that consumers are alerted to the specific tamper-resistant feature of the package. The labeling statement is also required to be so placed that it will be unaffected if the tamper-resistant feature of the package is breached or missing. If the tamper-resistant feature chosen to meet the requirement in paragraph (b) of this section is one that uses an identifying characteristic, that characteristic is required to be referred to in the labeling statement. For example, the labeling statement on a bottle with a shrink band could say “For your protection, this bottle has an imprinted seal around the neck.”

(d) Request for exemptions from packaging and labeling requirements. A manufacturer or packer may request an exemption from the packaging and labeling requirements of this section. A request for an exemption is required to be submitted in the form of a citizen petition under §10.30 of this chapter and should be clearly identified on the envelope as a “Request for Exemption from Tamper-resistant Rule.” The petition is required to contain the following:

(1) The name of the drug product or, if the petition seeks an exemption for a drug class, the name of the drug class, and a list of products within that class

(2) The reasons that the drug product’s compliance with the tamper-resistant packaging or labeling requirements of this section is unnecessary or cannot be achieved

(3) A description of alternative steps that are available, or that the petitioner has already taken, to reduce the likelihood that the product or drug class will be the subject of malicious adulteration

(4) Other information justifying an exemption

(e) OTC drug products subject to approved new drug applications. Holders of approved new drug applications for OTC drug products are required under §314.70 of this chapter to provide the agency with notification of changes in packaging and labeling to comply with the requirements of this section. Changes in packaging and labeling required by this regulation may be made before FDA approval, as provided under §314.70(c) of this chapter. Manufacturing changes by which capsules are to be sealed require prior FDA approval under §314.70(d) of this chapter.

(f) Poison Prevention Packaging Act of 1970. This section does not affect any requirements for “special packaging” as defined under §310.3(1) of this chapter and required under the Poison Prevention Packaging Act of 1970.

Product tampering is not a new occurrence. However, as a direct result of several deaths in 1982 resulting from the malicious addition of cyanide to Tylenol Capsules this section was introduced into the CGMP regulations. The key elements of the regulation are:

1. It only applies to OTC products since these tend to be on open display with ready access to the public. It was considered that prescription products are maintained under the control of the pharmacist and consequently are less vulnerable to tampering. The exemption of insulin was for the same reason. The other excluded categories—dentifrices, lozenges and dermatological products—were considered to be less prone to potential tampering because of their inherent nature or their use.

2. No test methodology or effectiveness criteria were established. It was considered that the development of these would be difficult, time-consuming and probably highly controversial and would delay the introduction of tamper-resistant packaging—which an apprehensive public needed in order to retain confidence in this essential form of medication (OTC). Instead, some guidance was provided on currently available forms of tamper-resistant technology (see Compliance Policy Guide 7132 a.17). These included film wrappers, with certain restrictions and limitation; blister or strip packs; bubble packs; heat-shrink bands or wrappers but not wet shrink, which were considered re-usable; foil, paper or plastic pouches; bottle mouth inner seals; tape seals; breakable caps; sealed metal tubes or plastic blind-end heat-sealed tubes; sealed cartons but not glued seals; aerosol containers; sealed cans. The tamper-resistant feature may apply to either the primary or the secondary packaging.

Use of a tamper-resistant feature on the secondary package allows the consumer to examine the product for possible tampering before purchase. This obviously is a consumer benefit. However, any inadvertent damage to the feature during shipping or storage will result in refusal to purchase. Application to the primary container, or a bottle mouth seal, will preclude this possibility.

The Compliance Guide does not suggest that any application of the above features will automatically assure compliance with §211.132, but the manufacturer should be able to demonstrate effective use of the technology. Conversely, other technologies are not excluded.

3. Two-piece hard gelatin capsules have been most vulnerable to tampering since once the contents have been replaced it is unlikely that the consumer will detect the differences, especially if the contents are a white powder. Use of bead formulations, especially if colored, increases security. The regulations now require that such OTC capsules have two tamper-resistant features. Two-piece capsules can have the two halves sealed and this is considered acceptable as one

of the two features. Because of this inherent higher vulnerability some manufacturers have ceased to provide this form of dosage, and some companies have introduced gelatin-coated tablets that look like capsules. These provide the consumer with ease of swallowability of the smooth elongated tablets and the strong medicine perception of a capsule.

The vulnerability of capsules to tampering was further evidenced by two further deaths and one serious illness resulting from tampering with Sudafed Capsules in 1991. The tampering was crude and relatively obvious. A foil packaging (blister) had been cut; the tampered capsules were larger and did not have the company logo or name; the contents were a yellow powder rather than white granules. This incident demonstrated that except at times of high public awareness, some of the public do not examine products for their tamper-evident features. However, in 1994 the FDA proposed that in the future all OTC capsules must be sealed in addition to the two other tamper-resistant features. To date no Final Rule has been issued.

4. The tamper-resistant feature is to be “distinctive by design or by use of an identifying characteristic.” This is to preclude the possibility of removal of the feature and replacement by a commonly available material. An aerosol package is considered to be distinctive by design, as would be a sealed can. Overwraps and seals usually require a distinctive characteristic such as the company logo or the product name. A generic expression such as “Factory Sealed” may not be sufficiently specific. A further concern relates to the possibility of taking a bottle mouth seal from a wide mouth bottle, cutting it down to size and gluing it to the mouth of a narrower neck bottle. Manufacturers must use their judgment.

5. Labeling is to include specific reference to the tamper-resistant feature used and must be sufficiently explicit that a malicious replacement can be identified by the consumer.

6. Tamper-resistant packaging components are to be treated identically to other components (Compliance Policy Guide 7132.14). Those coming into direct contact with the drug product are subject to the container and closure provisions of the CGMP Regulations (Subpart E). Other tamper-resistant components are subject to the appropriate provisions of Subpart G; in particular, any components with labeling information would need to comply with the provisions for labeling including accountability.

At the present time the currently available technologies do provide significant protection to the consumer but products are not tamper-proof. Additionally some tamper-resistant features, such as neck bands and breakable caps, may impact adversely on the ease of openability of the package. Whereas the majority of tamper-resistant features impart a physical barrier to entry it is anticipated that future developments will rely heavily on technologies, such as microencapsulated inks, which do not affect ease of opening. However, whatever technology is used

it must be applied effectively by the manufacturer and supported by an informed and alert consumer.

§211.134 DRUG PRODUCT INSPECTION

- (a) Packaged and labeled products shall be examined during finishing operations to provide assurance that containers and packages in the lot have the correct label.
- (b) A representative sample of units shall be collected at the completion of finishing operations and shall be visually examined for correct labeling.
- (c) Results of these examinations shall be recorded in the batch production or control records.

Compliance with the intent of this subsection requires that inspection and documentation procedures continue throughout the labeling-packaging operation to prevent incorrect components or procedures from being utilized. The majority of these on-line inspections are often performed by suitably trained production personnel, with QC confirming compliance with the defined inspection procedures and performing periodic audit. Sampling of controlled substances carry special responsibilities as to limitations on number taken, stored and security thereafter.

ON-LINE INSPECTION PLAN

The on-line inspection procedure should be statistically designed and is usually based on the classification of the inspected items as “defective” or “non-defective.” The aim of the system is to identify the types of defects that occur so that appropriate action can be initiated to determine and eliminate their cause and enable an objective decision to be made on the disposition of each packaged batch.

Defects, any nonconformance with specification, may be classified according to their seriousness.

Critical defect: one with a high probability of adversely impacting on the effectiveness of the product. Examples include incorrect product in the container, incorrect label, missing label, incorrect batch number or expiry date, incorrect carton.

Major defect: one with a low probability of adversely impacting on the effectiveness of the product. Examples include low fill volume, partly legible batch number or expiry date, missing carton.

Minor defect: one unlikely to have any impact on product effectiveness. Examples include poor printing on tablets or capsules, off-center or dirty labels.

The sampling plan, inspection level, and acceptance criteria will be based on product use and performance history and will be approved by Quality Control. Typical acceptance levels for each type of defect could be critical 0%, major 0.65%, or minor 2.5%. However, attempts should be made to identify the causes of any defects and to eliminate them, thereby resulting in reduction in acceptable defect levels and improvement in quality. It is interesting to note that the quality-conscious health-care industry still operates in the percentage defects range (parts per hundred), while some other industries, such as electronics, operate in the parts per million range.

Records will note the number and types of defects found, the time, and further specify the exact defect (i.e., off-center label). All critical defects should normally be reported immediately to departmental management, who will initiate additional inspection to ascertain the extent of the problem and to eliminate critically defective items from stock. A 100% inspection of all stock packed since the previous acceptable inspection is usually regarded as essential. If further critical defects are discovered it may be necessary to suspend production until the cause has been identified and corrected. If, during the course of the packaging run, it is observed that it is likely that the number of major or minor defectives will eventually result in a rejection number the production supervisor or manager should be informed so that appropriate action can be taken to rectify the situation. All such actions should be recorded and will go into the batch record.

Repetition of deviations, especially those classified as critical or major, is an indication that the equipment involved is not operating satisfactorily—maintenance, adjustment, or even replacement may be required. Alternatively, the problems could be caused by unacceptable variability in the packaging components. This may require modification of specifications and review with suppliers.

§211.137 EXPIRATION DATING

- (a) To assure that a drug product meets applicable standards of identity, strength, quality, and purity at the time of use, it shall bear an expiration date determined by appropriate stability testing described in §211.166.
- (b) Expiration dates shall be related to any storage conditions stated on the labeling, as determined by stability studies described in §211.166.
- (c) If the drug product is to be reconstituted at the time of dispensing, its labeling shall bear expiration information for both the reconstituted and unreconstituted drug products.

- (d) Expiration dates shall appear on labeling in accordance with the requirements of §201.17 of this chapter.
- (e) Homeopathic drug products shall be exempt from the requirements of this section.
- (f) Allergenic extracts that are labeled “No U.S. Standard of Potency” are exempt from the requirements of this section.
- (g) New drug products for investigational use are exempt from the requirements of this section, provided that they meet appropriate standards or specifications as demonstrated by stability studies during their use in clinical investigations. Where new drug products for investigational use are to be reconstituted at the time of dispensing, their labeling shall bear expiration information for the reconstituted drug product.
- (h) Pending consideration of a proposed exemption, published in the Federal Register of September 29, 1978, the requirements in this section shall not be enforced for human OTC drug products if their labeling does not bear dosage limitations and they are stable for at least 3 years as supported by appropriate stability data.

When the CGMP regulations were introduced there was considerable comment regarding the need for expiry dating. Subsequently, some concessions were made with respect to OTC products [see (h)]. The arguments against expiry dating essentially suggested that if it could be demonstrated that a product passed through the distribution chain within its acceptable life then there should be no need to display an expiry date on the product. This argument would seem to have little merit when it is known that stock rotation in the trade cannot be guaranteed and that consumers having purchased a product may not completely use it and will probably be unable to remember when it was purchased. One of the authors has personally identified products over 15 years old in the marketplace. Consequently there would seem to be very good reasons for expiry dating of all pharmaceutical products.

The need for expiration dating has consistently created problems with respect to clinical trials of new drugs being investigated. Frequently these products are supported by parallel stability studies and have only limited historical data that may be inadequate to predict a shelf-life. These products are distributed to clearly identified individuals and consequently recovery is easy. Industry has indicated that it is inappropriate and unnecessary to apply an expiration date to such clinical samples provided there are ongoing stability studies and a commitment to recover products from the trials if necessary. This was recognized and subsection (g) was incorporated into the regulations.

The USP solicited comments on the possible benefits and disadvantages of having only two expiry dates in each year, say June and December. The benefits are that it might make it easier for the trade to monitor stocks and identify those near the end of shelf-life. However, this could still be done with the existing method of expiry dating; any units shown to expire during the following six

months should be marked for early sale, or returned to supplier for destruction. The downside of such an approach would be that for relatively unstable products this could lead to significant reduction in shelf-life. For example, a product manufactured in November 1989 with a 24-month shelf-life would be required to show expiry in June 1991, an effective life of only 19 months—a reduction of 20 percent. Fortunately, this did not gain acceptance.

Products for reconstitution will show two separate shelf-lives: first an expiration date after which the unconstituted product should not be used, and second, the maximum period during which the reconstituted product must be used.

The exemption for homeopathic products is interesting since it appears to be based on two facts: the inability to quantitatively evaluate the low levels of ingredients in such products and the inability to relate effectiveness to quantitative composition. While both statements are correct, it might still be considered, by reputable homeopathic producers, that some restriction on shelf-life, while not proven to be essential, would certainly not be detrimental to the product user.

The approaches used to establish shelf-lives will be addressed in Chapter 10 (§211.166).

HEALTH-RELATED CLAIMS AND DIETARY SUPPLEMENT LABELING

The Dietary Supplement Health and Education Act of 1994 amended the FFDC Act to define somewhat the nature of health-related statements that could appear in the labeling of such products as defined (21 USC 343). It also established the Commission on Dietary Supplement Labels as an independent agency within the executive department. Their charge was an interesting one that reflects the tremendous growth of the commonly called “health food” industry: It was to conduct a study on, and provide recommendations for, the regulation of label claims and statements for dietary supplements, including the use of literature in connection with the sale of dietary supplements and procedures for the evaluation of such claims.

A reading of FDA regulatory proposals to implement this statute have irked the manufacturers and distributors of a broad spectrum of products including vitamins, minerals, botanicals, amino acids, and related substances and derivatives, because it would inhibit their promotional efforts. (See in example 63FR23, 624; 63FR45,427.) Thus while up to now the concerns of those who supported the Congressional enactment of DSHEA have been with FDA’s attempts to narrow by regulation the thrust of 21USC343®, there is little doubt that the FDA will seek eventually to do more than review the labeling of these products. Even though placed in the aura of foods rather than drugs, the FDA will feel the need to ascertain that the labeled contents of dietary supplements meet their claimed descriptions of ingredient content. At present FDA emphasis has been on truthful

language that does not suggest the product is intended to prevent, treat or mitigate a disease. The manufacturers, having been permitted by Congress to communicate truthful and not misleading information to consumers regarding the health-related benefits of dietary supplements, will use reason, strength and organization to hold their position. See also 21USC343® (3) (B) and FDAMA in relevant parts; 21CFR101.14.

REFERENCE NOTE FOR CHAPTER:

The Dietary Supplement Health and Education Act of 1994, Young and Stolzer, 12 Food, Drug, Cosmetic and Medical Device Law Digest 16 (1995), Volume 6 (1998), Young and Wiener.

A most recent attack upon that portion of the recently effective FDAMA, shown in relevant part in the Appendix A hereto, has culminated in a final order of the United States District Court for the District of Columbia in *Washington Legal Foundation v. Henney*, Civ. Action No. 94-1306 (RCL) substantially favoring the plaintiff's position concerning dissemination of off-label use information for approved drugs and medical devices. Thus both the statutory thrust and the FDA 1998 implementing regulations particularized by the Court, Judge Royce C. Lamberth, are found unconstitutional and unenforceable as of July 28, 1999.

To the manufacturers who want to disseminate certain off-label devices, this means the laborious requirements of the Act at 21 USC 360 aaa through 21 USC 360 aaa-6 need not be complied with. Put in simpler form, if I am a drug and/or device company that distributes journal reprints or medical textbooks that describe and discuss my product's use in a manner not included in my approved product labeling, I need not submit a sample of the off-label information to the FDA before I make it available to the medical professionals that might so prescribe its use; nor need I file with the FDA or commit to file, a supplementary NDA for those off-label indicators.

Further I need not disseminate in conjunction with the journal reprint or medical textbook a copy of the approved package insert; a statement (if applicable) that other products are approved for the off-label use noted in the disseminated material, nor a bibliography of other articles discussing the off-label use. The FDA had also required the manufacturer to submit a list biannually of all such articles and reference textbooks distributed during the prior 6 month period and a list of the categories of medical providers to whom distribution was made, and this job was also eliminated by Judge Lamberth's order.

So what remains in the light of the order appears the choice of materials which are limited to either articles published in bona fide peer-reviewed professional journals or reference texts or portions of same, published by a bona fide independent publisher. Of course the material must be pertinent to a drug or

device already approved or otherwise legally marketed for a different use, and aimed only at physicians or other medical professionals.

The information disseminated must not of itself be false or misleading and should carry the company's disclosure of its own interest and the fact that the new use discussed for the drug or devices has not been approved by the FDA.

The Court did leave open the possibility that in certain circumstances the FDA could prosecute such a dissemination on its statutory authority against "misbranding" under 21 USC 352 where it is obvious the company is using this method to avoid its responsibility under the Act, to provide full and accurate labeling containing safe and effective use of their product. These should not be used as "detail" aids for the sales force, nor in a manner that creates unfair competition.

It is interesting that the Court held that its decision declared unconstitutional, violative of the First Amendment, FDA policies as well as the Guidance Documents, *WLF v. Friedman* 36 F. Supp. 2nd 16, and subsequently the congressionally designed statutory language in support of those FDA policies.

Some years after publication of this 5th Edition, the U.S. Supreme Court may choose to hear an appeal from this order that is likely made by the Food and Drug Administration.

REFERENCE: LABELING CHAPTER, APPENDIX A

Washington Legal Foundation v. Friedman: a new era in off-label promotion? Phelps Wu, Samp, Atkinson, FDCMD Law Journal, Vol. 15. No. 3, Sept. 1998

EXAMPLES OF OBSERVATIONS FROM FDA 483 CITATIONS

1. The SOP uses the word should, in lieu of the word shall, in instances of mandatory actions in an SOP related to repackaging.
2. The firm uses cut flat labels. There is no record of the 100% visual inspection that was repeatedly performed.
3. There are no procedures for an evaluation of discrepancies found between the quantity of drug product finished and the quantity of labeling issued.

SUGGESTED READINGS

1. FDA, Current Good Manufacturing Practice in Manufacturing, Processing, Packing or Holding of Drugs; Revision of Certain Labeling Controls; Partial Extension of

- Compliance Date; Reopening of Administrative Record, *Fed. Reg.*, 59(147), 39255, 1994.
2. FDA, Tamper Evident Packaging Requirements for Over-The-Counter Human Drug Products, *Fed. Reg.*, 59(11), 2542, 1994.
 3. Laws Affecting Packaging—An Overview—Eric F. Greenberg, Vol. 9, No. 2 (May, 1997) Food Drug Cosmetic and Medical Device Law Digest.

Following study of this chapter, it might be helpful for staff review to discuss specific guides provided by the FDA to their field staff and others, that are pertinent as Regulatory Action Guidance.

POLICY ON HOMEOPATHIC DRUG LABELING FROM FDA COMPLIANCE GUIDES

LABELING

Homeopathic drug product labeling must comply with the labeling provisions of Sections 502 and 503 of the Act and Part 201 Title 21 of the Code of Federal Regulations (CFR), as discussed below, with certain provisions applicable to extemporaneously compounded OTC products. Those drugs in bulk packages intended for manufacture or preparation of products, including those subsequently diluted to various potencies, must also comply with the provisions of Section 502 of the Act and Part 201 (21 CFR 201).

General Labeling Provisions

Name and Place of Business: Each product must bear the name and place of business of the manufacturer, packer, or distributor in conformance with Section 502(b) of the Act and 21 CFR 201.1.

Directions for Use: Each drug product offered for retail sale must bear adequate directions for use in conformance with Section 502(f) of the Act and 21 CFR 201.5. An exemption from adequate directions for use under Section 503 is applicable only to prescription drugs.

Statement of Ingredients: Ingredient information shall appear in accord with Section 502(e) of the Act and 21 CFR 201.10. Labeling must bear a statement of the quantity and amount of ingredient(s) in the product in conformance with Section 502(b) of the Act, as well as 21 CFR 201.10, expressed in homeopathic terms, e.g., 1x, 2x.

Documentation must be provided to support that those products or ingredients which are not recognized officially in the HPUS, an addendum to it, or its supplements are generally recognized as homeopathic products or ingredients.

Established Name: The product must be in conformance with Section 502(e)(1) of the Act and must bear an established name in accord with Section 502(e)(3) of the Act and 21 CFR 201.10. Many homeopathic products bear Latin names which correspond to listings in the HPUS. Since Section 502(c) of the Act and 21 CFR 201.15(c)(1) require that all labeling be in English, the industry is required to translate these names from Latin

to their common English names as current labeling stocks are depleted, or by June 11, 1990, whichever occurs first. It is permissible for industry to include in the labeling both English and Latin names.

Container Size—Labeling Exemption: For those products packaged in containers too small to accommodate a label bearing the required information, the labeling requirements provided under Section 502 of the Act and 21 CFR 201 may be met by placing information on the carton or outer container, or in a leaflet with the package, as designated in 21 CFR 201.10(i) for OTC drugs and in 21 CFR 201.100(b)(7) for prescription drugs. However, as a minimum, each product must also bear a label containing a statement of identity and potency, and the name and place of business of the manufacturer, packer, or distributor.

Language: The label and labeling must be in the English language as described and provided for under 21 CFR 201.15(c)(1), although it is permissible for industry to include foreign language in the labeling, as well.

Prescription Drugs

The products must comply with the General Labeling Provisions above, as well as the provisions for prescription drugs below.

Prescription Drug Legend: All prescription homeopathic drug products must bear the prescription legend, “Caution: Federal law prohibits dispensing without prescription,” in conformance with Section 503(b)(1) of the Act.

Statement of Identity: The label shall bear a statement of identity as provided for under 21 CFR 201.50.

Declaration of Net Quantity of Contents and Statement of Dosage: The label shall bear a declaration of net quantity of contents as provided in 21 CFR 201.51 and a statement of the recommended or usual dosage as described under 21 CFR 201.55.

General Labeling Requirements: The labeling shall contain the information described under 21 CFR 201.56 and 21 CFR 201.57. For all prescription homeopathic products, a package insert bearing complete labeling information for the homeopathic practitioner must accompany the product.

OTC Drugs: Homeopathic

Product labeling must comply with the General Labeling Provisions above and the provisions for OTC drugs below, as current labeling stocks are depleted or by June 11, 1990, whichever occurs first.

Principal Display Panel: The labeling must comply with the principal display panel provision under 21 CFR 201.62.

Statement of Identity: The label shall contain a statement of identity as described in 21 CFR 201.61.

Declaration of Net Quantity of Contents: The label shall conform to the provisions for declaring net quantity of contents under 21 CFR 201.62.

Indications for Use: The labeling for those products offered for OTC retail sale must bear at least one major OTC indication for use, stated in terms likely to be understood by lay persons. For extemporaneously compounded OTC products, the labeling must bear

at least one major OTC indication for use, stated in terms likely to be understood by lay persons. For combination products, the labeling must bear appropriate indication(s) common to the respective ingredients. Industry must comply with the provisions concerning indications for use as current labeling stocks are depleted, or by June 11, 1990, whichever occurs first.

Directions for Use: See the General Labeling Provisions above.

Warnings: OTC homeopathic drugs intended for systemic absorption, unless specifically exempted, must bear a warning statement in conformance with 21 CFR 201.63(a). Other warnings, such as those for indications conforming to those in OTC drug final regulations, are required as appropriate.

Prescription/OTC Status

The criteria specified in Section 503(b) of the Act apply to the determination of prescription status for all drug products, including homeopathic drug products. If the HPUS specifies a distinction between nonprescription (over-the-counter (OTC)) and prescription status of products which is based on strength (e.g., 30x)—and which is more restrictive than Section 503(b) of the Act—the more stringent criteria will apply. Homeopathic products intended solely for self-limiting disease conditions amenable to self-diagnosis (of symptoms) and treatment may be marketed OTC. Homeopathic products offered for conditions not amenable to OTC use must be marketed as prescription products.

Home Remedy Kits: Homeopathic home remedy kits may contain several products used for a wide range of conditions amenable to OTC use. When limited space does not allow for a list of those conditions on the labels of the products, the required labeling must appear in a pamphlet or similar informational piece which is enclosed in the kits. However, as a minimum, each product must also bear a label containing a statement of identity and potency.

Following study of this chapter, it might be helpful for staff review to discuss specific guides provided by the FDA to their field staff and others, that are pertinent as Regulatory Action Guidance.

Sec. 450.500 Tamper-Resistant Packaging Requirements for Certain Over-the-Counter (OTC) Human Drug Products (CPG 7132a.17)

BACKGROUND:

* Requirements of the tamper-resistant packaging (TRP) regulations covering most OTC products were published by FDA in the FEDERAL REGISTER of November 5, 1982.

The regulations require that all OTC human drug products (except dermatologics, dentifrices, insulin and throat lozenges) (21 CFR 21.1.132), cosmetic liquid oral hygiene

products and vaginal products (21 CFR 700.25), and contact lens solutions and tablets used to make these solutions (21 CFR 800.12) be packaged in tamper-resistant packaging.

The packaging must use an indicator or barrier to entry that is distinctive by design (such as an aerosol container), or must employ an identifying characteristic (a pattern, name, registered trademark, logo, or picture). Further, the regulations require a labeling statement on the container (except ammonia inhalant in crushable glass ampules, aerosol products, or containers of compressed medical oxygen) to alert the consumer to the specific tamper-resistant feature(s) used. The labeling statement is also required to be placed so that it will be unaffected if a TRP feature is breached or missing.

An amendment to the TRP regulations for OTC human drug products published as a final rule in the FEDERAL REGISTER on February 2, 1989. The new requirements (21 CFR 211.132(b)(1) and (2)) are:

1. For two-piece, hard gelatin capsule products subject to this requirement, a minimum of two tamper-resistant packaging features is required, unless the capsules are sealed by a tamper-resistant technology.
2. For all other products subject to this requirement, including two-piece, hard gelatin capsules that are sealed by a tamper-resistant technology, a minimum of one tamper-resistant feature is required.

Manufacturers were given until February 2, 1990, to comply with the new requirements.

In addition, the Agency has re-evaluated currently available tamper-resistant packaging technologies and concluded that some technologies as designed or applied are no longer capable of meeting the requirements of the TRP regulations.

POLICY:

A. PACKAGING SYSTEMS

Manufacturers and packagers are free to use any packaging system as long as the tamper-resistant standard in the regulations is met. The TRP requirements are intended to assure that the product's packaging "can reasonably be expected to provide visible evidence to consumers that tampering has occurred."

Examples of packaging technologies capable of meeting the TRP requirements are listed below. The use of one of these packaging technologies does not, by itself, constitute compliance with the requirements for a tamper-resistant package. Packaging features must be properly designed and appropriately applied to be effective TRP.

1. **FILM WRAPPERS.** A transparent film is wrapped securely around the entire product container. The film must be cut or torn to open the container and remove the product. A tight "fit" of the film around the container must be achieved, e.g., by a shrink-type process. A film wrapper sealed with overlapping end flaps must not be capable of being opened and resealed without leaving visible evidence of entry.

The use of cellophane with overlapping end flaps is not effective as a tamper-resistant feature because of the possibility that the end flaps can be opened and resealed without leaving visible evidence of entry.

The film wrapper must employ an identifying characteristic that cannot be readily duplicated. An identifying characteristic that is proprietary and different for each product size is recommended.

Tinted wrappers are no longer acceptable as an identifying characteristic because of the possibility that their material or a facsimile may be available to the public.

2. **BLISTER or STRIP PACKS.** Dosage units (e.g., tablets or capsules) are individually sealed in clear plastic or plastic compartments with foil or paper backing.

The individual compartment must be torn or broken to obtain the product. The backing materials cannot be separated from the blisters or replaced without leaving visible evidence of entry.

3. **BUBBLE PACKS.** The product and container are sealed in plastic and mounted in or on a display card. The plastic must be torn or broken to remove the product. The backing material cannot be separated from the plastic bubble or replaced without leaving visible evidence of entry.
4. **HEAT SHRINK BANDS OR WRAPPERS.** A band or wrapper is securely applied to a portion of the container, usually at the juncture of the cap and container. The band or wrapper is heat shrunk to provide a tight fit. The band or wrapper must be cut or torn to open the container and remove the product and cannot be worked off and reapplied without visible damage. The use of a perforated tear strip can enhance tamper-resistance.

Cellulose wet shrink seals are not acceptable. The knowledge to remove and reapply these seals without evidence of tampering is widespread.

The band or wrapper must employ an identifying characteristic that cannot be readily duplicated. An identifying characteristic that is proprietary and different for each product size is recommended.

Tinted bands or wrappers are no longer acceptable as an identifying characteristic because of the possibility that their material or a facsimile may be available to the public.

5. **FOIL, PAPER, OR PLASTIC POUCHES.** The product is enclosed in an individual pouch that must be torn or broken to obtain the product. The end seams of the pouches cannot be separated and resealed without showing visible evidence of entry.
6. **CONTAINER MOUTH INNER SEALS.** Paper, thermal plastic, plastic film, foil, or a combination thereof, is sealed to the mouth of a container (e.g., bottle) under the cap. The seal must be torn or broken to open the container and remove the product. The seal cannot be removed and reapplied without leaving visible evidence of entry. Seals applied by heat induction to plastic containers appear to offer a higher degree of tamper-resistance than those that depend on an adhesive to create the bond.

Polystyrene foam container mouth seals applied with pressure sensitive adhesive are no longer considered effective tamper-resistant features because they can be removed and reapplied in their original state with no visible evidence of entry.

The Agency recognizes that technological innovations may produce foam seals that will adhere to a container mouth in a manner that cannot be

circumvented without visible evidence of entry. Container mouth seals must employ an identifying characteristic that cannot be readily duplicated. An identifying characteristic that is proprietary and different for each product size is recommended.

7. **TAPE SEALS.** Tape seals relying on an adhesive to bond them to the package are not capable of meeting the TRP requirements because they can be removed and reapplied with no visible evidence of entry.

However, the Agency recognizes that technological innovations may produce adhesives which do not permit the removal and reapplication of tape seals. In addition, tape seals may contain a feature that makes it readily apparent if the seals have been removed and reapplied. Tape seals must employ an identifying characteristic that cannot be readily duplicated.

8. **BREAKABLE CAPS.** The container (e.g., bottle) is sealed by a plastic or metal cap that either breaks away completely when removed from the container or leaves part of the cap attached to the container. The cap, or a portion thereof, must be broken in order to open the container and remove the product. The cap cannot be reapplied in its original state.
9. **SEALED METAL TUBES OR PLASTIC BLIND-END HEAT-SEALED TUBES.** The bottom of the tube is heat sealed and the mouth or blind-end must be punctured to obtain the product. A tube with a crimped end is capable of meeting the definition of a tamper-resistant feature if the crimped end cannot be breached by unfolding and refolding without visible evidence of entry.
10. **SEALED CARTONS.** Paperboard cartons sealed by gluing the end flaps are not capable of meeting the TRP requirements. However, the Agency recognizes that technological advances may provide sealed paperboard packages that meet the requirements of the TRP regulations.
11. **AEROSOL CONTAINERS.** Aerosol containers are believed to be inherently tamper-resistant because of their design. Direct printing of the label on the container (e.g., lithographing), is preferred to using a paper label which could be removed and substituted.
12. **CANS (BOTH ALL-METAL AND COMPOSITE).** Cans may be composed of all metal or composite walls with metal tops and bottoms. The top and bottom of a composite can must be joined to the can walls in such a manner that they cannot be pulled apart and reassembled without visible evidence of entry. Rather than attaching a separate label, direct printing of the label onto the can (e.g., lithographing) is preferred.

B. CAPSULE SEALING TECHNOLOGIES

Technologies for sealing two-piece hard gelatin capsules are available that provide evidence if the capsules have been tampered with after filling. Such sealing technologies currently in use include sonic welding, banding, and sealing techniques employing solvents and/or low temperature heating. These examples are not intended to rule out the development and use of other capsule sealing technologies. Manufacturers may consult with FDA if they are considering alternative capsule sealing processes.

Sealed capsules are not tamper-resistant packages. They are required to be contained within a package system that utilizes a minimum of one TRP feature.

C. TRP LABELING STATEMENT(S)

1. **BOTTLE (CONTAINER) CAPS.** In the past, some manufacturers have placed the TRP labeling statement on bottle caps. This practice is unacceptable in cases where it may be a simple matter to substitute another unlabeled bottle cap for the one with the tamper-resistant warning statement. Such an act could easily be accomplished without any apparent sign of tampering.
2. **PACKAGE INSERTS.** The practice of placing the TRP labeling statement solely on the product's inserts is not acceptable. While package inserts may be a useful supplement for consumer education purposes, they are not acceptable in lieu of label statements.
3. **CARTON/CONTAINER (OUTER AND INNER).** If the TRP feature is on an outer carton, the inner container (e.g., bottle) needs to bear a statement alerting the consumer that the bottle should be in a carton at the time of purchase. This policy applies only to situations where the inner container is so labeled that such a container might reasonably otherwise be displayed on the retail shelf without an outer carton.
4. **IDENTIFYING CHARACTERISTIC.** When a TRP feature is required to have an identifying characteristic, that characteristic needs to be referenced in the labeling statement (e.g., "imprinted" neck band). It is recommended that the labeling statement specifically identify the characteristic (e.g., imprinted with XYZ on the neck band).
5. **TRP FEATURE(S).** All required tamper-resistant features must be referenced in the labeling statement. When two tamper-resistant packaging features are used for unsealed two-piece hard gelatin capsules, both features must be referenced in the labeling statement. If one tamper-resistant packaging feature plus sealed capsules are used, the labeling statement must reference both the capsule seal and the tamper-resistant packaging feature.

REGULATORY ACTION GUIDANCE:

The TRP requirements are part of the current good manufacturing practice (GMP) regulations. Regulatory actions for deviations from these requirements should be handled in the same manner as any other deviation from the GMP regulations.

* Material between asterisks is new or revised *

Issued: 3/1/88

Revised: 5/21/92

Sec. 450.550 Control and Accountability of Labeling
Associated with Tamper-Resistant Packaging of
Over-the-Counter Drug Products (CPG 7132.14)

BACKGROUND:

Final rules (21 CFR 211.132) were published in the Federal Register on November 5, 1982 (47 FR 50442) (As corrected in 48 FR 1706) to provide tamper-resistant packaging requirements for certain OTC drug products.

Questions have been raised as to whether or not those parts of tamper-resistant packaging which may contain labeling, such as shrink seals imprinted with the product name, need to be controlled and reconciled, under the CGMP regulations. Questions have also been raised on the degree of control and accountability needed for parts of tamper-resistant packaging which may be part of the immediate container closure system or some other portion of the packaging.

POLICY:

Those portions of tamper resistant packaging which contain labeling, as defined in Section 201(m) of the FD&C Act, will be considered as any other labeling and, as such, are subject to the control and accountability provisions of Subpart G of the Current Good Manufacturing Practice Regulations.

Those portions of tamper-resistant packaging which contact the drug product are considered part of the container closure system and, as such, are subject to the control and accountability provisions of Subpart E of the CGMP regulations.

Those portions of tamper-resistant packaging which do not fall into the above categories will be considered as general packaging material, subject to the general controls for packaging contained in Subpart G of the CGMP regulations.

Issued: 3/1/83

Following study of this chapter, it might be helpful for staff review to discuss specific guides provided by the FDA to their field staff and others, that are pertinent as Regulatory Action Guidance.

Sec. 400.500 Identical or Similar Product Names (CPG
7132b.14)

BACKGROUND:

* Periodically different drugs, or drugs and other products, are marketed under identical brand names similar enough to cause confusion. It is apparent that a serious danger to

health could exist if a relatively mild drug or other product was dispensed in the place of a vitally needed antibiotic or vice versa. Other situations, equally serious could also be imagined. We investigated a complaint where a prescription drug was dispensed in the place of the prescribed vitamin with a similar name.

POLICY:

All instances of drugs of different composition including different dosage strengths being marketed under identical or similar brand names are regarded as serious violations of the Act due to the inherent potential health hazards. Regulatory action will normally be authorized.*

REGULATORY ACTION GUIDANCE:

The following represents criteria for recommending legal action to the * Division of Drug Labeling Compliance, HFD-310 *.

1. Identical Brand Names for Drugs of Different Composition. Section 502(i)(3) of the Act specifies that a drug shall be deemed to be misbranded if it is offered for sale under the name of another drug. This charge is to be used when regulatory action is recommended in this situation.
2. Similar Brand Names for Drugs of Different Composition. Section 502(a) of the Act specifies that a drug shall be deemed to be misbranded if its labeling is false or misleading in any particular. This charge is to be used when regulatory action is recommended in this situation.

The initial action of choice where no direct health hazard is involved is a * warning * letter. Recall is the initial action of choice in situations involving a hazard to health.

* Material between asterisks is new or revised *

Issued: 10/1/80

Revised: 5/22/87, 3/95

Sec. 400.600 Drugs—Declaration of Quantity of Active Ingredient by Both Metric and Apothecary Systems (CPG 7132.03)

BACKGROUND:

The USP and NF allow the simultaneous use of both the metric and apothecary systems to declare the quantity of active ingredients present in drug product labeling. Prior to USP XX and NF XV, the official compendia allowed the approximate equivalent of the exact quantity to be enclosed in parenthesis; such as Quinidine Sulfate 200 mg (3 grains).

On July 1, 1980 the USP XX and NF XV became official and requires that “Where expressed in both the metric and apothecary systems, statements of quantity or strength in the labeling of drug products shall utilize the exact equivalent.” (See inside back cover USP XX and NF XV.) Therefore the above example would now have to be modified to read Quinidine Sulfate 200 mg (3.086 grains).

POLICY:

USP and NF products shipped after 7/1/80 bearing a dual declaration will be considered misbranded if the exact equivalents are not used. However, as a general rule we are not prepared to initiate regulatory action of this violation alone. It may be included as a 502(g) charge only when other violations exist or it may serve as the basis for a Notice of Adverse Findings letter.

Issued: 10/1/80

Sec. 430.400 Urinary Preparations—Misbranding—Lack of Rx Legend and Claims (CPG 7132b.04)

POLICY:

We are not prepared to take regulatory action against the following class of products, particularly those which have been on the market for a significant period of time:

Products offered as urinary antiseptics, urinary analgesics, acidifiers, or diuretics; which are botanical mixtures, botanical with sodium biphosphate, ammonium chloride, phenazopyridine hydrochloride, or these chemicals alone or in combination.

Generally, we would prefer not to initiate regulatory action on such products based on misbranding charges (lack of Rx legend or inadequate full disclosure) until our medical position has been clarified.

If the product contains ingredients which may cause the drug to be dangerous to health when used as directed or if its labeling makes direct claims for more serious conditions, we might want to consider action. If you encounter such products which you believe warrant action, submit full labeling and formulation to Division of Drug Labeling Compliance, * HFD-310 * for advice before collecting samples for regulatory consideration.

* Material between asterisks is new or revised *

Issued: 10/1/80

Revised: 5/22/87, 3/95

SUB CHAPTER 435 MEDICAL GASES

Sec. 435.100 Compressed Medical Gases—*Warning Letters for Specific Violations Covering Liquid and Gaseous Oxygen* (CPG 7132a.16)

BACKGROUND:

* This CPG provides guidance for issuing warning letters to firms processing compressed medical gases in violation of the adulteration, misbranding, and/or new drug provisions of the Federal Food, Drug, and Cosmetic Act. *

Compressed medical gases, * including compressed medical oxygen and liquid oxygen, * are drug products regulated under 21 CFR 210 and 211.

* Section 201.100 requires that the labeling for prescription drugs (e.g., Oxygen U.S.P.) bear adequate directions for use. In this regard, the requirements of 201.100 would be satisfied if the article meets the labeling requirements described in the Federal Register of March 16, 1972, (37 FR 5504) entitled “Oxygen and its Delivery Systems, Proposed Statement of Policy.” Although this proposal was not finalized and is being revoked, the Agency continues to use it as a labeling guideline for medicinal oxygen.

Oxygen, U.S.P. would be misbranded if its label fails to indicate whether or not it has been produced by the air-liquefaction process as required by the United States Pharmacopeia (USP XXII).

Sec. 430.300 Labeling Shipping Containers of Drugs (CPG 7132b.13)

BACKGROUND:

Because of the pilferage problem, some firms prefer not to name the drugs on shipping containers, so that * their contents are not easily determined *. Questions have been raised as to whether or not the FDC Act requires mandatory label information on such shipping containers.

POLICY:

If the outer carton is used only to protect the goods during shipment and is stripped away by the consignee, then the FDC Act does not require any information to be stated on such shipping carton.

* Material between asterisks is new or revised *

Issued: 7/12/76 as 7132b.12

Revised: 10/1/80, 5/22/87

Sec. 450.400 Labeling and Distribution of OTC Drugs in Vending Machines (CPG 7132b.06)

POLICY:

There is no provision under the Federal Food, Drug, and Cosmetic Act which prohibits the sale of over-the-counter drug < > preparations in vending machines or in places other than drug stores. However, the article so vended must be in a full compliance with all the applicable sections of the Act.

The Act requires that certain mandatory labeling information must appear prominently, with such conspicuousness (as compared with other words, statements, designs or devices in the labeling) and in such terms as to render it likely to be read and understood by the ordinary individual under customary conditions of purchase and use. This means that the prospective purchaser must have an opportunity to read and take such information into consideration in reaching a decision whether or not to make the purchase. The vending machine should therefore bear a complete copy of the required labeling for the article being offered for sale or the article should be displayed in such a manner that the mandatory labeling can be viewed by the prospective purchaser.

< > Indicates material has been deleted

Issued: 10/1/80

Revised: 5/22/87

Although not covered in CGMP's, the staff might want to discuss comments on a new development as to labeling of present interest to FDA.

“OFF LABEL” INFORMATION AND LABELING

In simple terms, the FDA has consistently maintained up to fairly recent times, that any description of the purpose, indications, dosage, method of use for a product that was in any way attributable to the licensed labeler of that product, must in no way vary from the approved labeling. If it was variant and attributable to the manufacturer, distributor, supplier who placed the product with its original approved label and labeling into the interstate or international commerce, the product was violative of the misbranding and new drug sections of the Federal Food, Drug and Cosmetic Act and likely subject to all statutory remedies applicable.

In recent times, with the galaxy of possibilities of informing potential users and prescribers of pharmaceutical, such as the Internet, television, scientific meetings, forums, and publications, the FDA enforcement mechanism has been overtaxed. To complicate matters, when the FDA has sought to administer its remedies on perceived violations,

regulatees, or those the FDA regarded as regulatees, have resisted with sophisticated legal support.

Attorneys defending against FDA interference, in for example, distribution of drugs for off-label use, have enlisted the First Amendment of the U.S. Constitution, which prohibits the government's repression of free speech in all but highly qualified circumstances that have been described by the United States Supreme Court.

Federal courts have shown increasing sensitivity and sympathy for such arguments. In *Washington Legal Foundation v. Friedman*, District Court Judge Royce Lambeth rejected the argument of the FDA that the First Amendment should not apply to the promotional language of a pharmaceutical manufacturer, since the assignment to qualify and monitor such speech had been legally given them by Congress many decades prior. For the FDA, a major problem was that by various techniques of writing and enforcing regulation, they had moved their primary legislative assignment of governance over labels and labeling into the more controversial area of advertising. The Federal Trade Commission had major legislative support for supervision of advertising given by Congress at a time when both medication and the means of promotion were far less sophisticated and diverse.

So Judge Lambeth, examining the FDA position under more modern, and even more lenient, standards of government restrictions on advertising, was bound to be critical of the FDA's position and found it in conflict with the drug distributor's rights under the First Amendment. Their confidence shaken, following his decision, the FDA claimed that the Food and Drug Modernization Act of 1997 had cured the circumstances underlying his rejection (the text of that Act is cited elsewhere in this volume). The final word on this task taken by the FDA has not yet come from the courts, but judicial tenor seems to indicate that the FDA will need to be careful in selecting a situation to challenge. By choosing a gross violation of the rule with profound economic benefit for the manufacturer or distributor, and less than great advantage for the prescriber and the consumer, they may gain favorable judicial attitude.

However, when new uses that either save or improve immensely the quality of life are discovered by "outsiders," scientists in academia, governmental epidemiologists, and the like, it would almost seem that duty demanded that pharmaceutical manufacturers provide such information to the public via their professional intermediaries. Whether they do that by answering inquiries through their professional employees, providing legally reprinted journal articles that have been independently written and reviewed by the "outsiders," or supporting scientific and medical seminars in a "hands-off" manner, they seem on pretty solid ground. A further admonition in what they might distribute under such circumstances, that "FDA approval of their product's labeling does not include the uses, doses or methodology described" by the "outsiders," would also indicate a "non-promotional" character to the act.

In general, commercial speech such as product labeling is protected if it is not false or misleading, carry the stigmata of "misbranding," and does not involve unlawful activity. Nonetheless, a federal agency is on firmer ground for regulating commercial speech if by doing so it advances a substantial government interest in a direct and material way that reflects the least restrictive means of enforcement [*Central Hudson Gas v. Public*

Service Commission 447US557 (1980)]. That is why the FDA will likely seek a strong case for challenge, since commercial speech prosecutions tend to be fact driven. Uniform and consistent regulation is however essential to allow domestic pharmaceutical and device producers to compete in the present global economy.

See also [Chapter 11](#) below.

9

Holding and Distribution (Subpart H)

This brief chapter is concerned only with procedures within warehousing and distribution. Testing and release of products for distribution will be found in Chapter 10, §211.165, Testing and Release for Distribution, and in Chapter 11, §211.196, Distribution Records.

§211.142 WAREHOUSING PROCEDURES

Written procedures describing the warehousing of drug products shall be established and followed. They shall include:

- (a) Quarantine of drug products before release by the quality control unit.
- (b) Storage of drug products under appropriate conditions of temperature, humidity, and light so that the identity, strength, quality, and purity of the drug products are not affected.

As for components, containers and closures, quarantine of drug products does not require rigid physical separation. The degree of separation necessary is dependent upon other steps to ensure that quarantined product is not used prematurely. An effective paper or computer control system is acceptable. The emphasis must be on whether the system does prevent premature distribution. If it does,

the system, no matter how nonrestrictive, is acceptable; if it does not, the system, no matter how rigorous the physical separation, is not acceptable.

Traditionally there have been two types of warehouse storage conditions:

1. Ambient conditions. For many products an adequate shelf-life can be determined that encompasses the relatively wide range of conditions that constitute “ambient.” Local and national weather records are available which provide data on temperature ranges. Maintenance of actual temperature data in a warehouse provides the assurance that the assumptions made in determining shelf-life continue to be met.

Humidity and light are rarely controlled, or even monitored, since product packaging is usually designed to take these two conditions into account.

2. Refrigerator and freezer. Certain products that are relatively unstable at ambient conditions require storage at lower temperatures. Appropriate equipment or areas must be provided and the conditions monitored to confirm compliance with the prescribed storage requirements.

Recently the FDA has begun to insist that all products should be labeled with defined storage conditions; the previously assumed position that if no special storage requirements were stated then ambient conditions would apply was being challenged. One approach used by industry was to declare “store at controlled room temperature” (15–30°C) with supporting stability data at 25°C. This seemed appropriate since there are data available to demonstrate that nowhere in the United States do climatic conditions consistently reach 30°C (day and night, 365 days a year). However, the FDA is making this an issue and in some instances insists that supporting stability data should be at 30°C. This has the effect of shortening the product shelf-life, which could be significant.

During the International Conference on Harmonization (ICH) review of stability testing conditions (more details in §211.166), there was discussion on whether 25°C (based on climatic zone criteria) or 30°C (based on USP definition of controlled room temperature, CRT, and some extreme temperatures in parts of the United States) was the most suitable condition. The USP then revised its definition of CRT to “a temperature maintained thermostatically that encompasses the usual and customary working environment of 20° to 25°C (68° to 77°F); that results in a mean kinetic temperature calculated to be not more than 25°C; and that allows for excursions between 15° and 30°C (59° and 86°F) that are experienced in pharmacies, hospitals and warehouses.

This redefinition appeared to help resolve the stability testing condition issue, which was agreed at $25 \pm 2^\circ\text{C}$. However, there is still no agreement with the FDA on how to express CRT on product labeling. The USP definition is too long for many labels and is difficult, if not impossible, to evaluate when product

may be stored in several consecutive locations—plant warehouse, distribution warehouse, retail storeroom.

A second potential problem associated with the declaration of “controlled room temperature” storage is that most warehouses do not have adequate heating and ventilation systems to maintain such conditions; on occasion the temperature may exceed 30°C for short periods. Unless warehouses expend considerable money to introduce cooling systems to accommodate these relatively infrequent occurrences, it would be possible for them to be cited by the FDA for noncompliance. It is hoped that the availability of warehouse climatic data and suitable stability data will be an adequate alternative. However, many companies have now expended the capital to install air conditioning systems, especially since the introduction of the revised USP definition of CRT.

§211.150 DISTRIBUTION PROCEDURES

Written procedures shall be established, and followed, describing the distribution of drug products. They shall include:

- (a) A procedure whereby the oldest approved stock of a drug product is distributed first. Deviation from this requirement is permitted if such deviation is temporary and appropriate.
- (b) A system by which the distribution of each lot of drug product can be readily determined to facilitate its recall if necessary.

Distribution records must be constructed and procedures established to facilitate recall of defective product. A requisite of the system is approval and specific release of each lot of drug by the quality control function before distribution can occur. This control of finished goods for shipment allows only those drugs into commerce that have been shown by testing to conform to appropriate requirements.

The manufacturer must maintain records of all distribution transactions involving in-process or finished goods. All records should be indexed by either the manufacturing batch-lot number of the packaging control number as a means of accountability until the shipment passes from the direct control of the manufacturer. This type of indexing permits an efficient determination of the receiver of a lot to be recalled since only one shipment record need be examined. Depending on the marketing procedures of the individual company, distribution records may list shipments to consignees for packaging or labeling, or to an independent distributor, a wholesaler, a retail pharmacist, a physician, or possibly the ultimate consumer.

A variety of distribution recording systems may be utilized. Two of the more commonly used approaches are to record the lot or control number on the

retained copies of the shipping invoices or to record the dates on which each lot commenced distribution. This latter approach has disadvantages in that it does not readily accommodate the redistribution of small amounts of returned goods or the occasional need to distribute part lots out of sequence.

Many U.S. companies also distribute products to their foreign affiliates. The distribution records should also include these transactions. This can become complicated if distribution from the United States is to a central international distribution center and the U.S. operation has no records of the final distribution. In these situations the U.S. QA function should evaluate and audit the central international distribution center operation and confirm the adequacy of its systems and controls.

The distribution process also includes other considerations. It must be arranged so that a first in/first out movement of product occurs. This requirement is consistent with the intent of the stability and expiration dating policy. The distribution system must include provisions in order that this movement is achieved. Exceptions to this requirement that may be permitted should be described in written procedures.

All distribution records should be maintained for a minimum 3-year period after the distribution process for any control number has been completed. If expiration dating is used for a product, distribution records must be maintained at least for 1 year past the expiration date of the product [see §211.180(b)].

EXAMPLES OF OBSERVATIONS FROM FDA 483 CITATIONS

1. No procedures available describing distribution of oldest stock first or any record of batch numbers entering distribution.
2. Products requiring specific storage conditions, 59–86°F, were stored in a non-air-conditioned warehouse at 90°F.
3. No defined quarantine area for incoming finished drug products to be repacked.

10

Laboratory Controls (Subpart I)

§211.160 GENERAL REQUIREMENTS

(a) The establishment of any specifications, standards, sampling plans, test procedures or other laboratory control mechanisms required by this subpart, including any change in such specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms, shall be drafted by the appropriate organizational unit and reviewed and approved by the quality control unit. The requirements in this subpart shall be followed and shall be documented at the time of performance. Any deviation from the written specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms shall be recorded and justified.

In some instances specifications and test methods are dictated by official compendia such as the USP. Although these compendia procedures are the final arbiters for drugs and components listed in them, a manufacturer is allowed to substitute other procedures or automated equipment provided the results are comparable to those obtained using the official methods. In the event of a dispute or query the official methods are to be applied.

Any compendial product must comply with the compendial specifications unless the noncompliant parameter is clearly stated on the label (Compliance Policy Guide 1732a.03). The USP monographs provide useful guidance on the

typical contents of monographs for drug substances, excipients and dosage forms. Recently there has been increased emphasis from both USP and FDA to provide more details of impurities in bulk drug substances. This includes both the expected impurities from the synthesis or degradation of the bulk drug, usually limited to 2% and with the main impurities identified, and volatile solvent residues.

Where compendial specification and methods are not available, the manufacturer must develop his own based on current scientific practices.

Material and product specifications and test methods for new products are often generated by the research and development department. This is acceptable provided they are ultimately approved by quality control before implementation. Once a specification and methodology are included in a new drug application (NDA or ANDA) changes can only be made after prior approval by the FDA—except for tightening of specifications. FDA reviewing chemists are becoming increasingly critical of proposed specifications that are wider than the results seen in development batches. The reason for this is obvious—if the toxicology and clinical data were generated on batches with narrower specifications there may be no justification for wider ranges. This can create a dilemma for industry, since the earlier batches (for toxicology and clinical studies) may have been small-scale batches produced by R&D chemists. Later, full-scale production may involve different equipment, operators rather than researchers, and different sources of some materials. It may be impossible, due to time and financial constraints, to perform this early evaluation work on a commercial scale. Also, the processes may still be under development. Consequently, if commercial specifications need to be wider than those seen during development, some supporting data will be required.

ICH has provided guidance on specifications for impurities in new drug substances. Impurities were classified under several headings:

1. Organic impurities—actual or potential impurities likely to arise during synthesis, purification or storage. Sources include starting materials, reagents, by-products, intermediates and degradants. Impurities present at above 0.1% are to be characterized. Below 0.1%, characterization is not expected unless there is reason to expect undue toxicity.
2. Inorganic impurities—reagents, catalysts, heavy metals, charcoal, filter aids. These are usually evaluated by compendial methods and apply compendial limits.
3. Solvents—remaining from the process. Tests and limits are usually those included in the compendia. For other solvents, toxicity should be taken into account in defining appropriate limits.

Change controls must be designed into the approval procedures, thereby ensuring that no changes are made without quality control review and approval.

The requirement to document any act at the time of performance appears to preclude the use of intermediate or temporary recording of data such as weighings into notebooks that are discarded after transcription of the information into the formal system. Such intermediate records are acceptable if retained. However, wherever possible data should be recorded directly into the final format, eliminating the possibility for transcription errors.

Any deviations from written procedures must be recorded and be properly evaluated. The reason for the deviation should be identified and it should be determined that it will have no adverse impact on the drug product. Approval for any deviation should be by a suitably qualified individual—usually supervisor or manager.

(b) Laboratory controls shall include the establishment of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling and drug products conform to appropriate standards of identity, strength, quality and purity. Laboratory controls shall include:

(1) Determination of conformance to appropriate written specifications for the acceptance of each lot within each shipment of components, drug product containers, closures, and labeling used in the manufacture, processing, packing, or holding of drug products. The specifications shall include a description of the sampling and testing procedures used. Samples shall be representative and adequately identified. Such procedures shall also require appropriate retesting of any component, drug product container, or closure that is subject to deterioration.

(2) Determination of conformance to written specifications and a description of sampling and testing procedures for in-process materials. Such samples shall be representative and properly identified.

(3) Determination of conformance to written descriptions of sampling procedures and appropriate specifications for drug products. Such samples shall be representative and properly identified.

Whereas subsection (a) deals with the drafting and approval of any specifications, standards, sampling plans and test procedures, subsection (b) applies to the application of these to components, containers, closures, in-process materials, labeling, and drug products.

The procedures are to be scientifically sound and appropriate. Where possible, established specifications and test methodology such as USP will be applied. Otherwise a knowledge of the composition, potential impurities (synthesis intermediates, solvent residues, heavy metals, etc.) and breakdown products should be taken into account. The specifications should be designed to control any such impurities within acceptable levels and to monitor trends. As indicated previously, the application of “action levels” that are based on historical data and are

more rigorous than the specifications is a useful and practical way of highlighting adverse trends and bringing them to the attention of quality control management.

A common practice is to set the action levels such that 95% of all acceptable results will fall within these levels; the exceptional 5% will then be highlighted. In-process control action levels for physical parameters such as tablet weight or fill volumes are more usually approached by way of control charts.

CONTROL CHARTS

The use of control charts to monitor processes is illustrated by a typical application to tablet weight. The master control chart is set up with target weight, warning limits, and action limits.

For a new product, with no available historic data, control levels may be calculated from the USP criteria for “Uniformity of Dosage Units.” In-process testing involves weighing a composite of 10 tablets at a determined frequency, often every 15 minutes. The control limits would calculate to the target weight $\pm 6\% + \sqrt{10}$, or $\pm 1.9\%$. Warning and action levels could be set arbitrarily inside the target $\pm 1.9\%$ level.

Once a product is in production, the available data can be used to calculate new warning and action levels. Warning levels are frequently set at ± 2 standard deviations, with ± 3 standard deviations being used as the action level. Tighter controls may be applied where formulation and process show this to be practicable.

The operator, on weighing the composite of 10 tablets, records the data on the control chart. Where a machine delivers tablets from two stations (left and right) each side should be sampled and reported separately. When a result is outside of the warning levels, a resample should be taken and also be recorded, suitably marked to denote it is a resample result. If the results fall between warning and action levels no action may be necessary unless there is a developing adverse overall trend in results. If outside of action levels, the tablet press should be adjusted to bring the process back under control. A new sample should then be taken to confirm that the corrective action was effective. When results fall outside of the control limits the press should be stopped until the cause of the problem has been evaluated. In this case it may be necessary to quarantine production since the previous acceptable weight check until the evaluation is complete; these tablets may eventually have to be rejected.

Tablet compression equipment is now available that is self-adjusting and that automatically records tablet weight data and analyzes trends.

The test methods used may vary for different applications. For example, in-process test methods performed in production areas by production personnel may need to be more robust than those performed by laboratory personnel; product release methods may not need to include evaluation of breakdown compo-

nents which will be necessary for stability evaluation; nonavailability of equipment or servicing may result in different methods in different countries.

The effectiveness of test methodology is further dependent on two additional factors. First, the methods must be written in sufficient detail that no interpretation is necessary; asking an adjacent person to confirm an interpretation is no confirmation at all. If there is any doubt the query should be raised with quality control management and the procedure should be rewritten. Second, only trained individuals must be allowed to perform testing—this obviously should apply to all operations within pharmaceutical production.

Sampling requirements may also vary with component or product history. Comments on reduced testing and supplier validation were included earlier (§211.84).

The regulations also require retesting of components, closures, or containers that may be prone to deterioration. Testing should be restricted to evaluation of parameters known or expected to deteriorate during storage. As an example, for aspirin the evaluation of free salicylic acid would probably be adequate. This subject was addressed in [Chapter 6](#) (§211.87).

Confirmation of conformance to specifications usually involves two groups within the quality control department. The analytical or laboratory function is responsible for sampling and testing while a quality assurance unit reviews the resulting data and conclusions. This review by quality assurance forms part of the overall batch review procedure.

(b)(4) The calibration of instruments, apparatus, gauges, and recording devices at suitable intervals in accordance with an established written program containing specific directions, schedules, limits for accuracy and precision, and provisions for remedial action in the event accuracy and/or precision limits are not met. Instruments, apparatus, gauges, and recording devices not meeting established specifications shall not be used.

Calibration of equipment is an important, even critical, aspect of test methodology. Calibration programs should define who is responsible for the calibration, the frequency, how the calibration is to be performed and action to be taken if the equipment is found to be outside acceptable ranges.

In some instances calibration programs are contracted out to third parties. The responsibility for calibration must still reside with someone within the manufacturer's organization. That person must approve the calibration procedure, the acceptance criteria and the frequency. Calibration results must be recorded; it is not sufficient to report that the equipment is acceptable.

Frequency usually is determined on the basis of experience and past performance. Any equipment found to be outside of acceptable operational ranges must be taken out of service until it is returned to normal performance. Additionally, the potential impact of such equipment on testing performed since the previous

calibration needs to be evaluated. The potential implications of this are extensive. For example, an analytical balance that is serviced and calibrated every three months that is found to be significantly inaccurate might place in jeopardy some of the analytical results generated since the previous calibration. The rechecking of all analytical results would involve a significant amount of work. However, the recording of the specific pieces of equipment used for production and testing (§211.105) will narrow the field. To avoid or at least minimize the possibility outlined in the example above, it is usual to perform more frequent mini-calibrations. Although less comprehensive, and not as adequate as calibrations, these do provide a high degree of assurance that equipment is performing satisfactorily. Additional calibrations should be initiated if there is reason to suspect that equipment may not be performing satisfactorily.

§211.165 TESTING AND RELEASE FOR DISTRIBUTION

(a) For each batch of drug product, there shall be appropriate laboratory determination of satisfactory conformance to final specifications for the drug product, including the identity and strength of each active ingredient, prior to release. Where sterility and/or pyrogen testing are conducted on specific batches of short-lived radiopharmaceuticals, such batches may be released prior to completion of sterility and/or pyrogen testing, provided such testing is completed as soon as possible.

(b) There shall be appropriate laboratory testing, as necessary, of each batch of drug product required to be free of objectionable microorganisms.

As a result of a court ruling against Barr Laboratories in 1993, FDA investigators increased their level of attention to laboratory operations. The main points relating to laboratory operations included:

- Inadequate evaluation of the cause of out-of-specification results.
- Use of an outlier test to discount failing results.
- Lack of a defined procedure to evaluate out-of-specification results.
- Long delays in completion of the evaluation of failures—a maximum of 30 days was proposed.
- Frequency of failures (product history).
- Use of different samples to reevaluate a failing result, especially for content uniformity and dissolution.
- Averaging of results. For example, three assay values of 89, 90, 91 cannot be averaged to allow release of a product with a 90% minimum assay specification.
- Samples taken from blends were too large. They should be not more than three times the active ingredient dosage size.

- Sampling blends after they have been transferred to drums is not an acceptable alternative to sampling from the blender.
- For retrospective validation all batches produced in the designated time frame must be included unless there was a non-process-related error.
- Ideally, 20–30 batches should be evaluated for retrospective validation.
- All retrospective validation batches must be made by the same process.
- Concurrent and prospective validation require at least three batches.
- Particle size distribution specifications should be included in validation studies.

While many of the rulings from Judge Wolin make scientific sense, it does seem inappropriate that they are then universally applied by the FDA as requirements for CGMP compliance. However, the Barr case and the increased activity of the FDA certainly stimulated industry to reappraise its laboratory operations.

The regulations require confirmation of conformance of drug products to specifications prior to release. Identity testing and assay of active ingredients by the quality control laboratory is specifically required. In-process data from production personnel may be acceptable for most other parameters, provided operators have been properly trained, have adequate equipment, and performance is audited. The availability of process validation data and process control data does not eliminate the need for finished product testing. This is somewhat at variance with the acceptance of parametric release as an alternative to sterility testing for terminally sterilized products (details presented in §211.167). However, for sterility testing to be statistically valid the sample size would be impracticable with a high probability of obtaining false-positive results.

An exception is made to the testing before release requirement for the sterility and pyrogen testing of short-lived radiopharmaceuticals. Since the test time may be a significant part of the product shelf-life, release prior to completion of testing is allowed. Obviously in such instances the process should be thoroughly validated and controlled to minimize the chance of a sterility or pyrogen failure.

The need to test each batch of product required to be free of objectionable microorganisms applies to both sterile products and to those products where specific organisms are to be absent (e.g., absence of *P. aeruginosa* and *S. aureus* in topical products). Products covered by this requirement include terminally sterilized products and aseptically processed products such as injections, and products produced under clean and hygienic conditions to exclude specific organisms and/or to minimize the level of microorganisms. The processing conditions for these products have been described earlier (§211.113).

The effective microbiological control of nonsterile products, where required, will usually include evaluation of levels of total microbial content, absence of specified organisms, presence of adequate levels of any added antimicro-

bial agent or preservative, and review of the environmental data generated during the process. The subject of sterility testing is addressed in §211.167.

(c) Any sampling and testing plans shall be described in written procedures that shall include the method of sampling and the number of units per batch to be tested; such written procedure shall be followed.

(d) Acceptance criteria for the sampling and testing conducted by the quality control unit shall be adequate to assure that batches of drug products meet each appropriate specification and appropriate statistical quality control criteria as a condition for their approval and release. The statistical quality control criteria shall include appropriate acceptance levels and/or appropriate rejection levels.

The need for written sampling and testing plans and definition of acceptance criteria is basic. Appropriate “action levels” should be built into the acceptance criteria. As emphasized elsewhere, it is important that any atypical situations are brought to the attention of sufficiently senior people so that appropriate actions can be initiated.

Where testing is delegated to production personnel there should be adequate supporting data to demonstrate that the personnel were adequately trained, that equipment is suitable and properly maintained and calibrated, and that the results obtained are equivalent to those obtained by quality control. Audit programs should be in place to confirm these points.

(e) The accuracy, sensitivity, specificity, and reproducibility of test methods employed by the firm shall be established and documented. Such validation and documentation may be accomplished in accordance with §211.194(a)(2).

Analytical testing plays a key role in the overall control of product quality, and consequently it is imperative that the methodology used should provide accurate and reliable results. Although this subsection specifically applies to drug products, it is obvious that method validation should be applied to all methods, wherever used—components, in-process, process validation, finished product release, and stability.

ANALYTICAL VALIDATION

The subject of analytical validation has been covered in numerous publications over the years. However, this section will primarily focus on the approach resulting from the ICH review that was published in the *Federal Register*, March 1, 1995 (pp. 11260–11262).

The first step in analytical validation is to ensure that the analytical method is defined in detail and includes any specific instructions or precautions (including

safety) that are required to enable different trained analysts to perform the method reproducibly.

Four different analytical applications were reviewed—identification tests, quantification of impurities, limit tests for impurities, and assay of actives or other key components of drug products. It was acknowledged that there are other important analytical procedures, including dissolution testing for drug products and particle size characterization of materials, but they were not addressed at this time.

Identification tests normally compare the sample under evaluation with a known reference sample standard. The methods are frequently spectrographic (IR/UV) or chromatographic, but some older methods involve chemical tests such as functional groups. Validation of identity tests is essentially confirmation of specificity (see Table 1).

Impurity tests may be either quantitative or limit tests, and different validation requirements apply. For limit tests, specificity and detection limits only may be required. For quantification the requirements are similar to those for assay methods (including those used for dissolution and content uniformity) except that for assay methods, detection and quantification limits do not need to be established since the methods are operating well in excess of these limits. Some additional detail on specific characteristics is provided below.

Table 1 ICH Validation Guideline

Type of analytical procedure; characteristics	Identification	Impurities purity test		Assay; content/potency dissolution; measurement only
		Quantitation	Limit	
Accuracy	—	+	—	+
Precision				
Repeatability	—	+	—	+
Intermediate precision	—	+ ^c	—	+ ^c
Reproducibility	—	— ^a	—	— ^a
Specificity	+	+	+	+ ^b
Detection limit	—	+	+	—
Quantitation limit	—	+	—	—
Linearity	—	+	—	+
Range	—	+	—	+

Note:—signifies that this parameter is not normally evaluated; + signifies that this parameter is normally evaluated.

^aMay be needed in some cases.

^bMay not be needed in some cases.

^cIn cases where reproducibility has been performed, intermediate precision is not needed.

Accuracy—defines the agreement between the true value and the value found in the testing.

Precision—defines the degree of variability in a series of measurements from multiple testing of the same homogeneous sample. Precision is usually expressed as a standard deviation or coefficient of variation. Three levels of evaluation of precision are defined:

- (a) Repeatability—relating to testing performed over a short time interval.
- (b) Intermediate precision—evaluations performed on different days with different analysts and possibly different equipment.
- (c) Reproducibility—relates to collaborative studies between laboratories. This evaluation is a measure of the robustness of the method since many variables are involved—different facilities, different equipment, different analysts, different reagents. This is a key element in analytical verification and confirmation that a new laboratory (e.g., QC laboratory) obtained equivalent results to the originator laboratory (e.g., R&D).

Specificity—confirms the ability of the method to evaluate the desired analyte in the presence of known other components: degradants, impurities, potential contaminants, and excipients. Frequently this is assessed by comparing results from “normal” material with those from stressed samples (heat, light, moisture, acid and/or base).

Detection limit—particularly important for limit tests.

Quantitation limit—relates to the lowest level that can be determined quantitatively with adequate accuracy and precision.

Linearity—applies only to methods involving quantification and involves the demonstration of a linear response over the range being evaluated. For example, an assay method may be evaluated only over the range of 85–115% of the specification since any results outside of these values would be out of specification.

Range—defines the upper and lower levels that have suitable levels of precision and accuracy. This is sometimes omitted since the linearity provides equivalent information.

Ruggedness—while not a specific requirement in the ICH approach, it is an additional measure of the reliability of the method when normal variabilities in the product or method are experienced. Product variables can include excipient levels, pH ranges for liquids, hardness of tablets (potential impact on dissolution). Analytical method variables could include extraction process, sample preparation, HPLC flow rate, wavelength, mobile phase composition. The potential impact of these variables may be examined using a matrix design approach.

An extension to the ICH text on “Validation of Analytical Procedures” (Draft 5-1995) provides additional guidance on how to perform the actual testing for specificity etc.

The validation and verification (technology transfer) protocols should include acceptance criteria and be approved. Any discrepancies from the agreed acceptance criteria need to be evaluated and explained.

Revalidation/reverification should be considered when there are changes to the analytical methods or equipment or to the product formulation. For complex or difficult analytical methods, new analysts may need to be trained using the verification protocol.

Validation and verification data must be reviewed and approved by responsible persons. In the case of new methods it is advisable to have sign off by both the method development unit (R&D) and the method receiving unit (QC). This acknowledges that the method has been transferred effectively.

(f) Drug products failing to meet established standards or specifications and any other relevant quality control criteria shall be rejected. Reprocessing may be performed. Prior to acceptance and use, reprocessed material must meet appropriate standards, specifications, and any other relevant criteria.

Failure to meet specifications or noncompliance with the approved process should result immediately in a rejection until the cause of the event and the future of the product is ascertained. Since products are in a quarantine status until released or rejected, it may be appropriate to retain this quarantine status, particularly if it is expected that the problem can be resolved quickly. If a quick resolution is not possible then transfer to reject status alerts planning that another batch may be required, which should take some urgency and pressure off those attempting to evaluate and resolve the problem. The approach to be used in evaluating an out-of-specification result should be clearly defined in an SOP. As indicated earlier, this area was one of the main issues in the Barr Laboratories case.

There are always three aspects to a noncompliance situation. The first thing to evaluate is the validity of the actual analytical result. The product was manufactured with released components, using a validated process involving trained personnel and consequently the out-of-specification analytical value may be due to analyst error.

The analytical failure should be reported to the section supervisor or manager. The critical steps in the analytical procedure should be reviewed with the analyst and an appropriate evaluation initiated. A typical decision path for such an evaluation is outlined below (and in [Figure 1](#)) immediately following.

1. Investigate laboratory and production records for an assignable cause.
2. If an assignable laboratory cause is identified and there is sufficient sample preparation remaining, the initial analyst (“A”) should repeat the analysis in duplicate.
 - (a) If both results pass, consider release.
 - (b) If one or both of the duplicate results fail, go to step 4 (assumes the possibility of analyst bias).

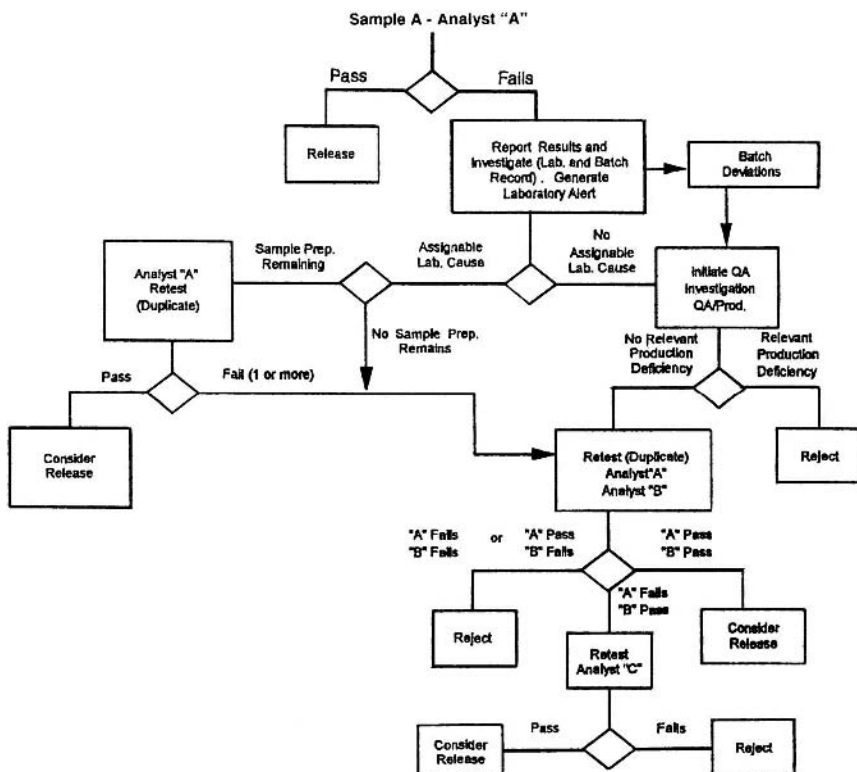


Figure 1 Decision path.

3. If there is no assignable laboratory cause but there is a relevant production deviation, reject the batch (it may be acceptable for rework).
4. If there is no assignable laboratory cause and no relevant product deviation or there is an assignable laboratory cause but no remaining sample preparation, retest in duplicate using two analysts ("A" and "B").
 - (a) If all results pass, consider release.
 - (b) If one or both results from "A" fail but both results from "B" pass, go to step 5.
 - (c) If one or both results from "B" fail, reject.
5. Retest in duplicate by another analyst ("C").
 - (a) If both results pass, consider release.
 - (b) If one or both results fail, reject.
6. Additional samples and testing may be necessary in order to resolve any problems that may be associated with analytical techniques, non-

representative sampling, or inhomogeneous material. Retesting of reference samples or previously released batches may be of value.

7. Where analyst bias or error is involved, retraining may be required.
8. If at any point in the decision path process it can be demonstrated that the result was invalid because of a specific identifiable error, that result can be ignored and a repeat analysis performed. The failing result must be reported with the supporting explanation. In rare cases an individual result may be excluded from the decision path if it deviates significantly from the average of the remaining values. The use of the statistical outlier approach was criticized in the Barr case, and consequently its application requires adequate scientific justification for FDA acceptance.
9. Duplicate analysis results must agree with the limits of precision defined during validation.
10. The final decision should not be a mechanistic application of the decision path. QC management must be involved and must apply its experience and knowledge of product history. Persistent or frequent failures are indicative of inadequate analytical method validation or verification, inadequate training, or inadequate process validation.

Second, how did the problem arise and what was the underlying cause? Unless the real cause is identified and appropriate corrective action initiated it is likely that the problem, or an equivalent one, will occur again. This was elaborated upon in §211.110. The third aspect is the future of the specific batch in question. If reprocessing is viable it must be done according to written and approved instruction, involving production and quality control. Where NDA/ANDA products are involved, the reprocessing should be in conformance with the approved NDA/ANDA methods, or FDA approval should be obtained. The reprocessed product must meet all of the product specifications. Additional data may also be required to confirm that the product will behave in a similar manner to a typical batch. Such additional data could include accelerated stability and ingredient degradation evaluation which might be included in a stability monograph but not in a release monograph.

Analyst training is not specifically referenced in §211.165. However, its importance is obvious. Training, which must be recorded, should include:

- Basic analytical techniques
- Specific methods where these are complex
- Good laboratory practices and relevant SOPs
- Laboratory safety
- New methods transferred from R&D (verification)
- Retraining for analysts whose results are atypical

§211.166 STABILITY TESTING

(a) There shall be a written testing program designed to assess the stability characteristics of drug products. The results of such stability testing shall be used in determining appropriate storage conditions and expiration dates. The written program shall be followed and shall include:

- (1) Sample size and test intervals based on statistical criteria for each attribute examined to assure valid estimates of stability;
- (2) Storage conditions for samples retained for testing;
- (3) Reliable, meaningful, and specific test methods;
- (4) Testing of the drug product in the same container-closure system as that in which the drug product is marketed;
- (5) Testing of drug products for reconstitution at the time of dispensing (as directed in the labeling) as well as after they are reconstituted.

(b) An adequate number of batches of each drug product shall be tested to determine an appropriate expiration date and a record of such data shall be maintained. Accelerated studies, combined with basic stability information on the components, drug products, and container-closure system, may be used to support tentative expiration dates provided full shelf life studies are not available and are being conducted. Where data from accelerated studies are used to project a tentative expiration date that is beyond a date supported by actual shelf life studies, there must be stability studies conducted, including drug product testing at appropriate intervals, until the tentative expiration date is verified or the appropriate expiration date determined.

(c) For homeopathic drug products, the requirements of this section are as follows:

- (1) There shall be a written assessment of stability based at least on testing or examination of the drug product for compatibility of the ingredients, and based on marketing experience with the drug product to indicate that there is no degradation of the product for the normal or expected period of use.
- (2) Evaluation of stability shall be based on the same container-closure system in which the drug product is being marketed.
- (d) Allergenic extracts that are labeled “No U.S. Standard of Potency” are exempt from the requirements of this section.

The purposes of stability studies are to predict and confirm product shelf life under the climatic conditions expected during trade storage, shipping, house storage, and use.

Before commencement of a stability evaluation the stability protocol should be written and approved—usually by technical services and QA. The key elements of a stability protocol include:

1. *Product name and packaging details.* The information should be sufficiently detailed to clearly identify the specific formulation(s) to be evaluated, the specific container/closure types (and sources), the batch size(s).

2. *Storage conditions.* For several years there was a lack of uniformity by the FDA on this subject. The Generic Division usually required “ambient” conditions to be 30°C whereas other divisions accepted 25°–30°C. Naturally this complicated the situation for companies, which then needed two sets of stability chambers. The rationale for the 30°C requirement appeared to be related to the then current USP definition of controlled room temperature (CRT) as 15°–30°C. It was stated that if the product labeling indicated storage at CRT then the stability should be performed at 30°C. Industry argued that the product, even when labeled with storage at CRT, would not be exposed to 30°C throughout its shelf-life. Eventually the issue was resolved (to some extent) via the International Conference on Harmonization (ICH) and the redefinition of CRT by the USP.

ICH, which used the climatic zone concept as part of the basis for its decisions, applied only to new chemical entities and also only to Europe, Japan, and the United States. The decisions were published in the *Federal Register* in September 1994.

The key points included:

- Stability storage conditions will normally involve long-term studies at $25^{\circ} \pm 2^{\circ}\text{C}$ with 60% RH $\pm 5\%$ with at least 12 months of data before filing; accelerated studies at $40^{\circ} \pm 2^{\circ}\text{C}$ and 75% RH $\pm 5\%$ with at least 6 months of data.
- Where “significant change” occurs during the 40°C accelerated study an additional intermediate station should be used, such as $30^{\circ} \pm 2^{\circ}\text{C}/60\% \text{ RH} \pm 5\%$. “Significant change” was defined as a 5% loss of potency, any degradant exceeding its specification limit, exceeding pH limits, dissolution failures using 12 units, failures of physical specifications (hardness, color, etc.).
- For less stable products the storage (and labeling) conditions may be reduced but the accelerated conditions should still be at least 15°C above those used for long-term evaluation.
- For products where water loss may be important, such as liquids or semisolids in plastic containers, it may be more appropriate to replace the high-RH conditions by lower RH such as 10–20%.
- The same storage conditions are to be applied for the evaluation of bulk drug substances. However, retest dates may be used instead of expiration dates.

The ICH proposal does not specifically address the position of samples during storage. This is especially important for liquid products where leakage and product closure interaction need to be evaluated. One approach is to store samples both upright and inverted but only to test the inverted samples. The upright samples may be used as controls in the event that problems are identified

with the inverted samples. For products with closures at two ends, such as pre-filled syringes and semisolids in tubes, storage horizontally is more appropriate.

As indicated earlier, these initial ICH proposals relate only to new chemical entities and the products made from these materials. However, the FDA has already begun to expect the same conditions for stability studies (with less data at the time of filing) for ANDAs and for supplements. ICH did commence evaluation of the conditions to be used and the data to be collected to support changes in product and production. It was considered that less data would be required since a “significant body of data on commercial production batches” would already exist. However, the parties involved could not agree on what constituted a significant body of data and the project was placed on hold. For completeness the key points in the nonagreed proposal are outlined next.

1. Change in manufacturing process of drug substance—3 months accelerated data on three batches of drug substance and 3 months of accelerated data on three batches of drug product—each manufactured from a different batch of drug substance.
2. Change in formulation of the drug product—ICH proposed 6 months of accelerated data on three batches plus 6 months of ambient data; FDA preferred 12 months of ambient data.
3. New strength of product (different composition, i.e., not simply compression at a different weight)—ICH proposed 6 months of accelerated and ambient data on two to three batches. FDA prefers 6 months of accelerated data on three batches and 12 months of ambient data.
4. Change in container and/or closure—ICH proposed 3–6 months of accelerated data on three batches. The FDA proposed 6 months of accelerated data and ambient data on three batches.

In November 1994 the FDA published a draft of its first proposal on manufacturing changes (SUSPAC). This related only to immediate-release solid oral dosage products. This did not define the amounts of stability data required to support a change but only the level of FDA involvement and approval required. Additional drafts relating to other dosage forms are due later.

The subject of light sensitivity/stability is still under active review, with Japan initially taking the lead role. While some progress was made, there is still some disagreement between Japan/United States and Europe. The latter authorities appear to be pushing for evaluation under extreme conditions.

The conditions used for storage of “ongoing” stability samples have not been universally agreed on. Some companies, either under their own initiative or under pressure from individual FDA reviewing chemists, have applied the 25°C/60% RH stations of the ICH guideline. This does allow easy comparison with the initial data. It also requires large amounts of stability cabinet storage space. Other companies have used warehouse storage with recording/reporting

of the conditions. This may be more typical of product exposure in the marketplace and includes some degree of “cycling” that does not occur in cabinets. However, because of the variability of warehouse conditions comparisons of data are less easy. As more warehouses are air conditioned/heated to comply with the USP definition of CRT this may reduce the variability. However, it seems likely that pressure will build for the use of cabinets for these samples.

3. *Number of batches to be evaluated.* Normally a minimum of three batches is required to provide a sufficient basis for shelf-life prediction. Development and stability batches may be used provided they are of the same formulations as the commercial product and they were processed in an equivalent manner. The ICH proposal requires stability data on three batches, two of which should at least be pilot scale (not less than 1/10th commercial scale and the same process or 100,000 tablets or capsules, whichever is the larger), and the third batch can be smaller. Stability results from laboratory-scale batches may be used only as supporting data. The first three commercial-scale batches are also to be included in the stability evaluation protocol.

For some drug products there can be a number of variants—different pack sizes, different strengths, some with the same formulation, and different packaging/closure arrangements. In such circumstances the extent of the stability evaluation can become enormous. To accommodate these situations, bracketing and matrixing approaches were introduced to reduce the amount of testing required.

Bracketing involves making conclusions about all levels of a parameter based on the evaluation of the extremes. Suggested applications include:

- Same formulation and container/closure system involving different container sizes and/or different fill volumes.
- Different strengths of the same formulation (e.g., different capsule sizes or different tablet weights from the same granulation).

Matrixing involves a statistical experimental design that allows only a fraction of the total number of samples to be tested at each sampling point. Since fewer tests are performed there is usually more variability in the data and a shorter predicted shelf-life may result. However, this can be “corrected” when more data eventually become available. Matrix designs should be applicable:

- For the same formulation in different strengths (same granulation).
- For different but closely related formulations.
- For different sources of bulk drug substance.

An example of a matrix design would be a tablet product produced in three strengths (same granulation, different compression weights) and packaged into three different bottle sizes. Three batches of granulation are produced, each of which is compressed into three sublots with the different compression weights.

Each of these nine sublots of tablets is then packaged into the three different bottle sizes—27 sets of stability samples. Testing is to be performed at 0, 3, 6, 9, 12, 18, 24, and 36 months.

A complete evaluation would therefore involve 27×8 (216) sets of testing. Three alternative matrix designs could be applied. In each of these all of the different combinations are tested at 0 and 36 months. In a complete one-third design, one-third of the samples are tested at each intermediate point, and in the complete one/two-thirds design one-third of the samples are tested at some points and two-thirds at others. The complete one-third design is depicted in Figures 2 and 3.

This matrix results in the testing of 108 samples—half of the total if all combinations had been tested. The number of samples tested could be further reduced by testing only one sample of each granulation batch (3 samples rather than 27) or one sample from each strength of each granulation batch (9 samples rather than 27).

Granulation batches: G1, G2, G3				
Compression weights: 100, 200, 300				
Packages: P1, P2, P3				
Test sample groups T1, T2, T3				
MATRIX				
Granulation Batch	Strength	Packages in group		
		T1	T2	T3
G1	100	P1	P2	P3
	200	P2	P3	P1
	300	P3	P1	P2
G2	100	P3	P1	P2
	200	P1	P2	P3
	300	P2	P3	P1
G3	100	P2	P3	P1
	200	P3	P1	P2
	300	P1	P2	P3

Figure 2 Matrix.

Test Group	Testing				
	Testing Interval (months)				
T1	0	3	12		36
T2	0		6	18	36
T3	0		9	24	36

Figure 3 Matrix design.

A matrix approach may also be applied to the actual tests performed on the samples—each test need not be performed at each test interval.

It is recommended that bracketing and matrixing proposals should be reviewed and agreed on with the FDA prior to introduction. With time and experience (FDA and industry) the need for this prior agreement should reduce.

4. *Test methodology.* The stability testing monograph need not include all of the criteria defined in the product release monograph. Only those parameters that are potentially susceptible to change during storage and that may impact on quality, safety, or efficacy need to be evaluated. However, the rationale for exclusion of the other parameters should be explained and supported. The characteristics evaluated will include actives; degradants; antimicrobial agents; antioxidants; and key physical characteristics such as dissolution, fragility, color, taste, moisture, and volume. Closure integrity may also be required; however, evaporation or leakage will normally show up in other tests. Functional effectiveness should also be evaluated: child-resistant closures; tamper-evident packaging; syringability for prefilled syringes; openability of containers. For tamper-evident packaging there are currently no generally accepted methods of evaluation, and in-house methods should be developed.

For parenteral or other sterile products, testing should include sterility assurance. This may be achieved by normal sterility testing, but because of the large number of samples evaluated during a stability protocol there would be some chance of a “false-positive” result which could create difficulties in interpretation. A validated closure integrity test may therefore offer a better approach and can be used with a larger number of samples if required. Recently FDA microbiologists appear to be favoring this approach. However, there are currently no universal closure-integrity test methods that have both industry and FDA support. This needs urgent resolution.

Some FDA reviewers have also been requiring pyrogen/endotoxin results both at time of manufacture and at expiration. It was difficult to understand the possible source of this endotoxin in a sterile product. Reputedly the predicted sources were elastomeric closures. The author is unaware of this ever being an issue, and it is hoped that this nonessential requirement will be eliminated.

5. *Test frequency should be adequate to demonstrate any degradation and to provide enough data points for statistical evaluation.* For the scale-up batches and the first three commercial batches testing is expected initially, at 3-month intervals during the first year, 6-monthly in the second year, and yearly thereafter. Some companies do not evaluate beyond 36 months. A different frequency may be more appropriate for ongoing stability evaluation (see later).

6. *Name and/or titles of those responsible for assessing the data.* Where possible, and appropriate, the data should be evaluated statistically to obtain the shelf-life.

Stability studies can be classified into three types:

1. Studies, usually under accelerated conditions to predict a tentative shelf-life for a new or modified product or process. For a new drug substance these studies usually commence with a preformulation evaluation. The effect of stress conditions such as temperature, humidity, light, acidity, and oxygen, can provide much useful information to the formulator. The potential interactive effects of the bulk drug and the anticipated dosage form excipients may also be evaluated. It should also be noted that any ingredient which interferes with the official assay of a USP product automatically makes the product noncompliant with that monograph—regardless of whether an alternate assay has been developed. Where degradation is observed, attempts should be made to identify the decomposition products, since this information could be of value later in developing analytical methodology for product stability studies.

The accelerated studies at elevated temperature on the dosage form should allow some extrapolation to provide a tentative shelf-life. The ICH guidelines allow extrapolation of 6 months data under accelerated conditions with 12 months data at 25°C/60% RH to predict a shelf-life of up to 24 months. Shelf-life in excess of 24 months should rarely be extrapolated from accelerated data. There are also some parameters such as dissolution, whose shelf-life performance cannot be predicted from accelerated study data. Consequently, any significant change in dissolution during accelerated studies should be a signal for caution until adequate real-condition data are available.

For changes in container closure, formulation, or material supplier, the FDA usually requires accelerated data comparing the revised product with the existing product plus a commitment to continue the stability study. The previously designated shelf-life may be retained if there are no observed differences. A similar approach should be used when reprocessed material is incorporated into a batch.

Where there is a change of manufacturing facility for the dosage form, but using the same process and similar equipment, 3 months

accelerated data may suffice, again with the commitment to monitor the first three commercial batches.

2. Studies under conditions appropriate to the market, or those defined in the product labeling, are used to provide real-time data for confirmation of the predicted tentative shelf-life. These studies are usually performed using controlled environmental cabinets. A typical warehouse may be an acceptable alternative provided temperature and humidity are recorded. For certain physical parameters such as dissolution, tablet fragility, and parenteral sterility, accelerated conditions may not provide useful data for extrapolation.

Where such studies demonstrate that the predicted tentative shelf-life was too optimistic it would be necessary to consider recall of released batches.

Real-time studies are also used to extend the defined shelf-life where the predicted value is found to be too pessimistic.

3. Stability studies on current production. Once the shelf-life is established it is necessary to evaluate some ongoing batches to confirm that current production is behaving in a similar manner. This is to detect the possible impact of any subtle or unknown changes to the components or process. In the event that a change is observed, it will be necessary to perform a root cause analysis.

At this stage there should be a considerable amount of available stability data that identify the shelf-life limiting factors. This will allow elimination of some tests. For example, with aspirin tablets if the initial assay was 98% (lower specification limit 90%) there would seem to be no value in repeating the assay if the free salicylic acid (FSA) is measured (upper limit 0.3%) since the FSA clearly measures breakdown of the aspirin. The frequency of testing should also relate to the shelf-life. It would seem unnecessary to test a product with a 5-year shelf-life every year and three data points, compared with previously studied batches, should be sufficient. Recently some FDA reviewing chemists have been requiring the same testing frequency as for new products (0, 3, 6, 9, 12, 18, 24, 36 months). This would seem to be scientifically unnecessary and to be a non-value-adding cost when there is already a stability database for the product.

The FDA is prepared to recommend action, such as a regulatory letter or seizure, if there is inadequate evidence to support the shelf-life (Compliance Policy Guide 7132a.04). Specific concerns include lack of sterility assurance; lack of, or noncompliance with, a stability program; absence of an expiry date; inadequate test methodology; lack of ongoing stability; lack of assurance of preservative effectiveness; distribution after expiration date.

The stability requirements for homeopathic products are less demanding than for other drug products. The levels of “active ingredients” are frequently so low that determination of degradation products, or even assay of the active itself, may not be practicable. The requirements allow examination for compatibility as an alternative to testing.

The immediate container and closure play an important role in the product shelf-life. They may accelerate degradation reactions, be an additive to or an absorbant of the drug substance, and be ineffective in protecting the contents from environmental conditions. Four types of containers are commonly analyzed for pharmaceutical preparations: glass, plastic, rubber (natural and synthetic), and metal. Each has characteristic properties which that should be recognized.

GLASS

Glass, because of its many variations and resistance to chemical and physical change, is the most commonly used container material. Several inherent limitations exist with glass:

1. Its alkaline surface may raise the pH of the pharmaceutical and induce chemical reaction.
2. Ionic radicals present in the drug may precipitate insoluble crystals from the glass (such as barium sulfate).
3. The clarity of the glass permits the transmission of high-energy wavelengths of light, which may accelerate physical or chemical reactions in the drug.

To overcome the first two deficiencies, alternate types of commercial glass, each possessing different reactive characteristics, are available. Borosilicate (USP type I) glass contains fewer reactive alkali ions than the other three types of USP-recognized glass. Treatment of glass with heat and/or various chemicals, as well as the use of buffers, can eliminate many ionic problems normally encountered. Amber glass transmits light only at wavelengths above 470 nm, thereby reducing light-induced reactions. When light sensitivity is a stability issue, the secondary packaging, with appropriate labeling, may provide adequate protection.

PLASTICS

These packaging materials include a wide range of polymers of varying density and molecular weight, each possessing different physical and chemical characteristics. Various additives to the polymeric material are often required to provide suitable characteristics for molding, to minimize impact damage or for color. As a result, each must be considered in relation to the pharmaceutical that will be

in contact with it to determine that no undesirable interaction occurs. Several problems are encountered with plastic:

1. Migration of the drug through the plastic into the environment.
2. Transfer of environmental moisture, oxygen, and other elements into the pharmaceutical formulation.
3. Leaching of container ingredients into the drug.
4. Adsorption or absorption of the active drug or excipients by the plastic.

Since each plastic possesses intrinsic properties, varying conditions and drug formulations must be tested to optimize stability of the final product by selecting the appropriate container. Again, chemical treatment of the material prior to use may reduce reactivity, migration characteristics, and transmitted light. It must be remembered that neither the drug nor the container should undergo physical or chemical changes that affect the safety and efficacy of the product. The use of light transmission by plastics as a measure of light protection is complicated by the fact that plastics are only semitransparent. Light that is admitted to the container is reflected and diffused back into the product so that light energy available to degradation processes is much higher than that which might be indicated by transmission characteristics. The proper test is a diffuse reflectance measurement. Appropriate testing procedures and specifications are given in the USP.

METALS

Various alloys and aluminum tubes frequently are utilized as containers for emulsions, ointments, creams, and pastes. These materials are generally inert to their contents, although instances of corrosion and precipitation have been noted with products at extreme pH values or those containing metallic ions. Coating the tubes with polymers, epoxy, or other material may reduce these tendencies but impose new stability problems on the pharmaceutical. The availability of new, less expensive polymers has sharply reduced the use of metal packaging components during the last few years.

RUBBER

The problems of extraction of drug ingredients and leaching of container ingredients described for plastics also exist with rubber components. The use of neoprene, butyl, or natural rubber, in combination with certain epoxy, Teflon, or varnish coatings, substantially reduces drug-container interactions. The pretreatment of rubber vial stoppers and closures with water and steam removes surface blooms and also reduces potential leaching that might affect chemical analysis, toxicity, or pyrogenicity of the drug formulation. The impact of additional treatments, such as siliconization to enhance movement of elastomeric components during handling in production or for plunger action in syringes, must also be evaluated.

§211.167 SPECIAL TESTING REQUIREMENTS

(a) For each batch of drug product purporting to be sterile and/or pyrogen-free, there shall be appropriate laboratory testing to determine conformance to such requirements. The test procedures shall be in writing and shall be followed.

(b) For each batch of ophthalmic ointment, there shall be appropriate testing to determine conformance to specifications regarding the presence of foreign particles and harsh or abrasive substances. The test procedures shall be in writing and shall be followed.

(c) For each batch of controlled release dosage form, there shall be appropriate laboratory testing to determine conformance to the specifications for the rate of release of each active ingredient. The test procedures shall be in writing and shall be followed.

Specific testing requirements for sterile products, ophthalmic ointments, and controlled release products are delineated in this section. These requirements are very general in nature and it is difficult to comprehend a need for this subsection.

As written, §211.167(a) requires testing to confirm sterility and where appropriate pyrogen testing on each batch of sterile or pyrogen-free product. The necessity for such testing would seem superfluous for terminally sterilized products prepared by the application of validated processes. The sterility test in these circumstances is more a challenge of the technique in the microbiology laboratory than an assurance of sterility. This was recognized by the FDA, which in 1985 approved the replacement of the sterility test by parametric release for certain large-volume parenterals. This was followed in 1987 by the issuance of a Compliance Policy Guide (7132a.13). This guide defined the criteria for parametric release:

1. Only terminally sterilized products may be considered.
2. The sterilizer validation should include:
 - a. Chamber heat distribution
 - b. Heat distribution for each load configuration
 - c. Heat penetration studies for the products
 - d. Lethality study using organisms with known resistance, usually *Bacillus stearothermophilus*
 - e. Presterilization bioburden—number of organisms and their resistivity to the cycle
 - f. Recording of all key cycle parameters—time, temperature, pressure
 - g. Demonstration of bioburden reduction to 10⁰ and a minimum safety factor of 6 logarithm reduction

3. Closure integrity validation should be performed on each container-closure system to ensure no ingress of organisms during the shelf-life.
4. Bioburden is required on each batch of product prior to sterilization. The resistance of any spore-forming organisms is to be measured and compared with those found during the validation study. It is also indicated that if such organisms had a higher resistance the batch would be considered nonsterile.
5. Biological or chemical indicators are to be used in each sterilizer load.

The detailed requirements of the Compliance Policy Guide essentially replace traditional sterility testing with an alternative sterility testing procedure; validation of the sterilization process forms only a part of this alternative procedure. The main points of concern include:

1. The F_0 concept does not appear to be accepted since the Guide states that “failure of more than one critical parameter must result in automatic rejection of the sterilizer load.” Critical parameters include time, temperature, and pressure, while heat-up and cool-down times are considered noncritical.
2. Evaluation of container-closure integrity would seem to be more appropriate to stability considerations and has no direct correlation with parametric release.
3. There would seem to be opportunity to eliminate the requirement for bioburden evaluation, including evaluation of microorganism resistance, on each batch of product if historical data shows little variability and the sterilization cycle involves significant overkill (e.g., $F_0 > 6$).
4. Without considerable validation evaluation, the use of chemical indicators in each load would not be reliable. The alternative, biological indicators, appears essentially to replace the traditional sterility test by an alternative version. With a validated process, shown to be operating under control, there would seem to be no need for biological indicators in each batch. Their use is superfluous. Although less prone to false-positives than sterility tests, their use prevents the opportunity for early batch release since an incubation period is still involved.

Perhaps the Guide represents a transition stage which may ultimately lead to true parametric release. However, this still has not occurred.

The special requirements for ophthalmic ointments relate to the potential presence of abrasive particulate matter. This is of obvious concern in such preparations and especially since metal tubes are frequently used for their packaging. The USP <751> includes specifications and methodology for the presence of metal particles in ophthalmic ointments. Although metal particles are considered to be the biggest risk, especially from metal tubes, it should be noted that §211.167(b)

refers more generally to “foreign particles and harsh or abrasive substances.” For products packaged in other configurations, such as plastic tubes, it would seem appropriate to apply the USP metal particle limits and to establish appropriate methodology to allow visualization of other particulate matter.

Subsection (c) refers to controlled release products and is somewhat generic in nature—“there shall be appropriate laboratory testing to determine conformance to the specifications for the rate of release of each active ingredient.” This is so obvious that the rationale for this specific inclusion is difficult to appreciate. Products with the same active ingredients may be formulated by different manufacturers to have different release patterns. This creates no problems with respect to drug registration but it does for the USP and for the consumer with respect to OTC products. The USP is moving toward generic-style monographs which define ranges for release rates at three or four time intervals: 0.125, 0.250, 0.500, and 1.00D, where D represents the dosing interval (e.g., 8 hours). Where possible the criteria defined in the USP for Drug Release (724) will be applied. This allows for different release patterns from different products. The release pattern would be presented on the product label, which allows the knowledgeable consumer some choice. At one stage the USP also suggested inclusion of blood level data on some OTC labels, but this was eventually dropped since it was unlikely to be of any real help to the consumer.

§211.170 RESERVE SAMPLES

(a) An appropriately identified reserve sample that is representative of each lot in each shipment of each active ingredient shall be retained. The reserve sample consists of at least twice the quantity necessary for all tests required to determine whether the active ingredient meets its established specifications, except for sterility and pyrogen testing. The retention time is as follows:

(1) For an active ingredient in a drug product other than those described in paragraphs (a) (2) and (3) of this section, the reserve sample shall be retained for 1 year after the expiration date of the last lot of the drug product containing the active ingredient.

(2) For an active ingredient in a radioactive drug product, except for nonradioactive reagent kits, the reserve sample shall be retained for:

(i) Three months after the expiration date of the last lot of the drug product containing the active ingredient if the expiration dating period of the drug product is 30 days or less; or

(ii) Six months after the expiration date of the last lot of the drug product containing the active ingredient if the expiration dating period of the drug product is more than 30 days.

(3) For an active ingredient in an OTC drug product that is exempt from bearing an expiration date under §211.137, the reserve sample shall be

retained for 3 years after distribution of the last lot of the drug product containing the active ingredient.

The regulations require retention of active ingredients but not of inactive ingredients. This relaxation for inactives was in response to comments that some materials are hazardous or unstable. However, samples of hazardous or unstable active ingredients are to be retained.

The rationale for retaining samples is to allow evaluation in the event of a complaint or query. Consequently, it is prudent to retain samples of all ingredients, active and inactive.

If a batch of ingredient is delivered on more than one occasion samples from each delivery are to be retained. This is in line with the evaluation of such deliveries.

(b) An appropriately identified reserve sample that is representative of each lot or batch of drug product shall be retained and stored under conditions consistent with product labeling. The reserve sample shall be stored in the same immediate container–closure system in which the drug product is marketed or in one that has essentially the same characteristics. The reserve sample consists of at least twice the quantity necessary to perform all the required tests, except those for sterility and pyrogens. Except for those drug products described in paragraph (b)(2) of this section, reserve samples from representative sample lots or batches selected by acceptable statistical procedures shall be examined visually at least once a year for evidence of deterioration unless visual examination would affect the integrity of the reserve samples. Any evidence of reserve sample deterioration shall be investigated in accordance with §211.192. The results of the examination shall be recorded and maintained with other stability data on the drug product. Reserve samples of compressed medical gases need not be retained. The retention time is as follows:

(1) For a drug product other than those described in paragraphs (b) (2) and (3) of this section, the reserve sample shall be retained for 1 year after the expiration date of the drug product.

(2) For a radioactive drug product, except for nonradioactive reagent kits, the reserve sample shall be retained for:

(i) Three months after the expiration date of the drug product if the expiration dating period of the drug product is 30 days or less; or

(ii) Six months after the expiration date of the drug product if the expiration dating period of the drug product is 30 days.

(3) For an OTC drug product that is exempt for bearing an expiration date under §211.137, the reserve sample must be retained for 3 years after the lot or batch of drug product is distributed.

The retention of batch samples of product allows evaluation in the event of complaints or queries. For large pack sizes, where product costs and storage

space could be a problem, it is acceptable to retain the samples in a smaller version of the immediate container-closure system. The actual storage conditions for retained samples are not defined. It would seem appropriate to use conditions which are reasonably related to those likely to be experienced by the commercial product. This would probably equate to warehouse conditions for products with no special storage requirements. However, this would not be appropriate for a product required to be stored in a refrigerator (see also §211.166).

The requirement for annual visual examination seems to have minimal value since most degradation effects are not visible. Should visible degradation occur it would be expected that pharmacists and consumers with overall access to greater amounts of product would be likely to observe the effect. Even accepting that all complaints are not reported, it would be expected that any significant occurrence would be noticed by the company who would be able to take appropriate action more rapidly than waiting for an annual sample inspection.

The FDA acknowledged that the evaluation of all retained batches was a time-consuming exercise. As a consequence, (b) was revised in 1994 to allow evaluation of a statistically selected number of batches only.

The FDA allows the annual review to be omitted if in so doing the integrity of the sample would be affected. For example, if a product is stored in a colored or translucent container that must be kept closed, then visual examination may be impractical.

The results of any visual examination may be held with other stability data and need not be entered into individual batch records.

§211.173 LABORATORY ANIMALS

Animals used in testing components, in-process materials, or drug products for compliance with established specifications shall be maintained and controlled in a manner that assures their suitability for their intended use. They shall be identified and adequate records shall be maintained showing the history of their use.

Minimum standards for the care and health of research and test animals are described in the following sources:

1. Animal Welfare Act (7 USC §§2131–2156).
2. Title 9, Code of Federal Regulations, §§1.1–11.41.
3. Good Laboratory Practice for Nonclinical Laboratory Studies, 21 CFR Part 58.
4. Guide for the Care and Use of Laboratory Animals, DHEW Publication No. (NIH) 78-23, revised 1978, U.S. Government Printing Office, Washington, DC, 017-040-00427-3, 1978.

In addition to these requirements, current interpretation of Good Manufacturing Practices would regard animals as sources of product contamination. Considerations such as separate facilities, constructed away from manufacturing areas, with closed water, waste removal, air conditioning, and other systems would, therefore, be ideal. If these are not possible due to construction or other limitations, animal areas should be segregated as far as possible from all production activities with closed air, water, and waste systems, as well as limited personnel access. The same standards of cleanliness prescribed for other work areas are also applicable to these spaces.

Record requirements for animals are necessary to maintain control of their use in experimentation, testing, or assay procedures. Data fields for individual animals should include:

1. Identification number or letter assigned to each animal or group of animals
2. Characteristics and description of animal
3. Source of animals (breeder, vendor)
4. Date of arrival
5. Age at arrival
6. How used
7. Date used

If the animal is to be used for repeated assay procedures, i.e., pyrogen testing, a time period sufficient to permit complete clearance of the drug and recovery of the test animal is required.

§211.176 PENICILLIN CONTAMINATION

If a reasonable possibility exists that a nonpenicillin drug product has been exposed to cross-contamination with penicillin, the non-penicillin drug product shall be tested for the presence of penicillin. Such drug product shall not be marketed if detectable levels are found when tested according to procedures specified in 'Procedures for Detecting and Measuring Penicillin Contamination in Drugs,' which is incorporated by reference. Copies are available from the Division of Research and Testing (HFD-470), Center for Drug Evaluation and Research, Food and Drug Administration, 200 C St. SW, Washington, DC 20204, or available for inspection at the Office of the Federal Register, 800 North Capitol Street, NW, Suite 700, Washington, DC 20408.

This regulation permits low-level contamination of drug products with penicillin. The permitted tolerance is at the "undetectable" level, using specific methodology. If there was proper control of all sources of cross-contamination, there would be no need for this testing, since it is required only if a reasonable possibility exists for such contamination.

If there is possibility of contamination of raw materials by penicillin because of its place of production or warehousing, it is appropriate for a manufacturer to require that the supplier test and certify that the material is not contaminated. If the possibility of contamination arises from the conditions of shipping, those conditions should be changed, or the manufacturer must test for the absence of contamination.

EXAMPLES OF OBSERVATIONS FROM FDA 483 CITATIONS

1. SOP uses a statistical outlier test to invalidate out-of-specification results; statistical outlier tests are inappropriate for use with validated methods.
2. Data acceptance/rejection was done selectively.
3. Stability testing SOPs contained no provision for increased testing of either additional lots or additional intervals or shortened intervals after confirmed stability failures.
4. There is no statistical analysis nor graphical representation of the firm's stability data in the annual product reviews.
5. There are no data to show that the methods used to analyze stability samples were validated as stability indicating with respect to acid and base hydrolysis, oxidation, thermal degradation, and photolysis.
6. There is no system in place that assures that senior management are made aware of problems that may affect product quality.
7. Failure to validate the software, which is used to collect raw data from the HPLC units, to integrate peaks, and to perform analytical calculations for assaying products.
8. The firm used the service of an outside microbiology laboratory for microorganism quantitation and identification. The laboratory had never been audited by the firm.
9. Chromatograms are run for an extended length of time without additional standard solution injections being made to check on the stability of the chromatographic system.
10. There are no criteria established for out-of-specification results defining at what points testing ends, product is evaluated, and rejected if results are not satisfactory.
11. Stability test failures not reported to the FDA.

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11

Records and Reports (Subpart J)

§211.180 GENERAL REQUIREMENTS

(a) Any production, control, or distribution record that is required to be maintained in compliance with this part and is specifically associated with a batch of a drug product shall be retained for at least 1 year after the expiration date of the batch or, in the case of certain OTC drug products lacking expiration dating because they meet the criteria for exemption under §211.137, 3 years after distribution of the batch.

(b) Records shall be maintained for all components, drug product containers, closures, and labeling for at least 1 year after expiration date or, in the case of certain OTC drug products lacking the expiration dating because they meet the criteria for exemption under §211.137, 3 years after distribution of the last lot of drug product incorporating the component or using the container, closure, or labeling.

(c) All records required under this part, or copies of such records, shall be readily available for authorized inspection during the retention period at the establishment where the activities described in such records occurred. These records or copies thereof shall be subject to photocopying or other means of reproduction as part of such inspection. Records that can be immediately retrieved from another location by computer or other electronic means shall be considered as meeting the requirements of this paragraph.

(d) Records required under this part may be retained either as original records

or as true copies such as photocopies, microfilm, microfiche, or other accurate reproductions of the original records. Where reduction techniques, such as microfilming, are used, suitable reader and photocopying equipment shall be readily available.

(e) Written records required by this part shall be maintained so that data therein can be used for evaluating, at least annually, the quality standards of each drug product to determine the need for changes in drug product specifications or manufacturing or control procedures. Written procedures shall be established and followed for such evaluations and shall include provisions for:

(1) A review of a representative number of batches, whether approved or rejected, and, where applicable, records associated with the batch.

(2) A review of complaints, recalls, returned or salvaged drug products, and investigations conducted under §211.192 for each drug product.

(f) Procedures shall be established to assure that the responsible officials of the firm, if they are not personally involved in or immediately aware of such actions, are notified in writing of any investigations conducted under §211.198, 211.204, or 211.208 of these regulations, any recalls, reports of inspectional observations issued by the Food and Drug Administration, or any regulatory actions relating to good manufacturing practices brought by the Food and Drug Administration.

The intent of subsections (a) and (b) is to have available records for review for a reasonable time after the expiration date of the product. The period chosen was based on FDA experience as to the time when the records are most likely to be needed. The prudent manufacturer will keep these records until the statute of limitations runs out for liability to the consumer.

In general, the regulations do not require retention of original records; retention of suitable true copies such as on microfilm is permissible, provided equipment for reading of the record and the making of hard copies is available. The records must be available at the location at which they were generated, but not necessarily stored there in hard form, if the record can be readily accessed on demand, such as from a data processor terminal or by electronic transmission.

It should be noted that the FDA does not have the authority to inspect records regarding the manufacture of nonprescription drugs that are not “new drugs” as defined in Section 201(p) of the Federal Food, Drug and Cosmetic Act. The FDA reviews records under its mandatory inspection authority contained in Section 704 of the act and further extended in the 1953 amendments contained in Public Law 82-217, which established section 704(a), and in the Drug Amendments of 1962 contained in Public Law 87-781 (1961). Note, however, that manufacture of any drug product without compliance to Good Manufacturing Practices makes the product adulterated under Section 301(b) of the Act and a federal crime under Section 303 of the Act. The FDA, therefore, if it had reliable information that a nonprescription or old drug product was being manufactured in viola-

tion of Current Good Manufacturing Practices, could obtain a search warrant that would authorize the inspection of the records to seek evidence regarding the alleged criminal offense.

In short, while the FDA does not have authority to inspect the records required under this subpart, or even inquire into the existence of such records for nonprescription drugs that are “not new,” the records may be obtained or their absence determined under a search warrant obtained on reliable information, such as provided by an FDA inspection, that there was violation of Current Good Manufacturing Practices in the production of the product.

Section (c) authorizes the FDA to copy the records and, by implication, to remove the copies from the premises. These copies are required to be released under the Freedom of Information Act, unless they contain information of such a nature that a request for release could be denied. Denial would usually be based on the prohibition of disclosure of “trade secret” information in FDA files in 21 CFR 20, particularly in Section 20.61.

Subsection (e) requires a review at least once a year of the quality standards for each drug product in order to determine needs for changes in specifications or controls. It also requires that written procedures shall exist for how the evaluation is to be made. It is suggested that a review schedule be set within the quality control unit in order that the burden of review is spread throughout the year.

The requirements for annual reporting are contained in 21 CFR 314.70 (d) and 314.81 (b)(2). The FDA has been concerned at the variability of submitted reports and in some instances the absence of data. In September 1994, CDER issued the “Guidance for Industry. Format and Content for the CMC section of an Annual Report.” The intent is to bring some degree of consistency to the reports, and also to provide more comprehensive information of changes effected that could help reviewers when evaluating supplements for changes. A standardized format is proposed, the content of which includes:

- Summary of new information. A brief summary of all changes to the application during the reporting period.
- Distribution data. The quantity of each product/pack size distributed with subdivisions for domestic and foreign distribution. There would seem to be little value in this requirement except if there was no distribution.
- Labeling. Details of any labeling changes and copies of all current labeling.
- CMC data. A list of approved chemistry, manufacturing, and control information. A prescribed format is provided. This is an extensive requirement. There should be (1) changes in the CMC section, to include compendial changes (with supporting verification data), formulation changes (plus a copy of the revised labeling), extension to expiration

date (with supporting stability data), changes in the container/closure system (with details of supplier and DMF reference, test data to demonstrate equivalency, commitment to long-term stability), and changes in test methods (with reason, validation, comparative data); and (2) stability report, for which a proposed format is provided.

The annual review of data should not be considered a bureaucratic exercise for the benefit of the FDA. It should be used by the management team as basic data to drive improvement. In addition to the data required by the FDA, management should review deviations, reworks, rejections, and complaints (and other customer feedback related to quality). The annual report should be the basis for a life-cycle approach to product quality. It provides important input for in-house pharmacoepidemiologic analysis.

Prior to 1994, §211.180(e)(1) required review of every batch, but the regulation was changed. With the current application of computerized systems such as LIMS, it is possible to continuously evaluate data for trends.

Subsection (f) speaks to FDA experience that corporate officials were not advised of potential or real adverse conditions uncovered by the firm's own quality assurance system or by the FDA. Corrective actions that might have been taken therefore were not established. Correspondence by the FDA regarding findings on inspection and recall are directed to the corporate officials, but not all items in Section 211.180(f) are necessarily the subjects of FDA inspection and recall. In a professionally managed QA/QC operation there should be a clearly written communications procedure that clearly identifies what quality issues are to be reported, to whom, and at what frequency—immediate, monthly, quarterly, annually. This is essential if senior management is to be involved in the drive for quality compliance and improvement. The subsection also enhances the ability of the corporate officers to carry out their very rigid legal duties to take action on conditions leading to drug adulteration as shown in *United States v. Park* (421 U.S. 658, 1975) and *United States v. Dotterweich* (320 U.S. 277, 1943).

§211.182 EQUIPMENT CLEANING AND USE LOG

A written record of major equipment cleaning, maintenance (except routine maintenance such as lubrication and adjustments), and use shall be included in individual equipment logs that show the date, time, product, and lot number of each batch processed. If equipment is dedicated to manufacture of one product, then individual equipment logs are not required, provided that lots or batches of such product follow in numerical order and are manufactured in numerical sequence. In cases where dedicated equipment is employed, the records of cleaning, maintenance, and use shall be part of the batch record.

The persons performing and double-checking the cleaning and maintenance shall date and sign or initial the log indicating that the work was performed. Entries in the log shall be in chronological order.

This section requires written designation of which equipment is “major.” The intent of the regulations is not to include small items such as ladles, scoops, stirrers, and spatulas. The exclusion of “nonmajor” items from the record-keeping requirement does not, however, exclude them from the requirements that they be properly cleaned.

Because the log is for a repetitive operation, the record may be initialed rather than signed. Note that a separate log, which may be a completely separately bound volume, or consecutive pages in a bound or loose-leaf format, or a number of individual records or logs is required for each piece of major equipment that is not dedicated to the manufacture of a single product. The issue of signatures and initials has involved considerable industry–FDA interaction. As new computerized technology became available it was possible to move to paperless control of manufacturing processes. These computerized controls had several advantages over manual systems:

- More consistent control.
- Only approved (trained) personnel could perform a process.
- Processing could be prevented until any prior steps or checks were performed.
- Precise recording of the times of operations were possible.

Electronic signatures/initials frequently involve a personal password and a personal magnetic card with a secure system to manage allocation and review.

For some time the FDA disagreed with this approach and stated that signatures and initials must be handwritten. After an extensive review, involving other areas of government and industry, the FDA in 1994 issued a Proposed Rule that stated that electronic recording was an acceptable alternative (see Suggested Reading, 2). The Proposed Rule, which will eventually appear in CFR Part 11, “considers electronic records, electronic signatures and handwritten signatures executed to electronic records, to be trustworthy, reliable, and generally equivalent to paper records and handwritten signatures executed on paper.”

This acceptance of electronic alternatives has application at various points in the CGMP regulations.

Routine maintenance and adjustment need not be logged, although it is strongly suggested, because it is just this information which will be needed to show compliance with §211.67. The data referring to cleaning should also be incorporated into the appropriate batch record so that they are readily available for review prior to release. For units which are fully dedicated, the information may be part of the batch record. Even though there is this exemption for dedicated

equipment, it is suggested that the log be kept since it is easier to retrieve a history of cleaning and maintenance from a record dedicated to logging such information than it is from perusal of individual batch records. An annual review of equipment function is implicit in §211.180(e)(1).

§211.184 COMPONENT, DRUG PRODUCT CONTAINER, CLOSURE, AND LABELING RECORDS

These records shall include the following:

- (a) The identity and quantity of each shipment of each lot of components, drug product containers, closures, and labeling; the name of the supplier; the supplier's lot number(s) if known; the receiving code as specified in §211.80; and the date of receipt. The name and location of the prime manufacturer, if different from the supplier, shall be listed if known.
- (b) The results of any test or examination performed (including those performed as required by §211.82(a), §211.84(d), or §211.122(a) and the conclusions derived therefrom.
- (c) An individual inventory record of each component, drug product container and closure and, for each component, a reconciliation of the use of each lot of such component. The inventory record shall contain sufficient information to allow determination of any batch or lot of drug product associated with the use of each component, drug product container and closure.
- (d) Documentation of the examination and review of labels and labeling for conformity with established specifications in accord with §§211.122(c) and 211.130(c).
- (e) The disposition of rejected components, drug product containers, closure, and labeling.

The regulations require identification and recording of the name of the producer of components, product containers, closures, and labeling. Where the name of the producer is not known, the supplier is to be identified. This provides for the use of agents who may be unwilling to divulge their source of supply. However, without knowledge of the actual producer, it is not possible to evaluate the producer's facility or integrity and the agent may be tempted to switch producers for various business reasons. This could have significant impact especially with respect to raw materials, which may have different impurity profiles, different processability and different stability. Consequently, purchasing through such agents should be discouraged.

As with every aspect of the regulations, documentation is required—in this instance, reporting of test results and conclusions reached and dispositions.

Subsection (c) requires the keeping of individual inventory records for product containers and closures (but not other packaging materials), which will

allow identification of the specific lots used in each batch of drug product. Components are to be treated similarly but additionally require reconciliation of usage. These procedures are important in the effective evaluation of production problems and consumer queries. Action levels should be established for component usage, based on historical data, and any usage falling outside of these levels should be brought to the attention of management and be investigated.

§211.186 MASTER PRODUCTION AND CONTROL RECORDS

(a) To assure uniformity from batch to batch, master production and control records for each drug product, including each batch size thereof, shall be prepared, dated, and signed (full signature, handwritten) by one person and independently checked, dated, and signed by a second person. The preparation of master production and control records shall be described in a written procedure and such written procedure shall be followed.

The master production and control records for each drug product describe all aspects of its manufacture, packaging and control. The preparation by one competent individual and independent verification of its correctness with endorsement and dating by both parties is a basic concept of Good Manufacturing Practices. Competence infers the possession of sufficient knowledge, through academic training and experience, to allow proper compilation and checking. The two individuals involved with each master record are required specifically to sign, not initial, the document. The preamble to the CGMPs infers that it is not always possible to decipher an initial. The same is true for some signatures and it may be advisable to additionally type or print names below signatures on documents.

Specific reference is made to the requirement for master production and control records for each batch size. For manufacturing and packaging operations this is important in order to eliminate the need for recalculation of quantities of components, packaging materials, and in-process samples. This is not relevant for control documentation where specifications and finished product testing are not usually related to batch size.

This is the only section of the CGMPs that specifically uses the term “handwritten” with respect to signature or initial. The proposed revision to 21 CFR Part 11 retains this requirement but allows the use of more recent technology. “The act of signing with a writing or marking instrument such as a pen, or stylus is preserved. However, the scripted name, while conventionally applied to paper may also be applied to other devices which capture the written name.” The second, check, signature is not required to be handwritten and the electronic alternative proposed in Part 11.3 would be acceptable. With the current and projected

usage of computerized documentation systems it is hoped that the FDA will allow these alternative approaches to signatures and initials while the regulations are being finalized.

Surprisingly, with so much emphasis on signatures and initials, largely as a basis for potential legal cases, there is no specific mention, in either the original CGMPs or the proposed revision to Part 11, that any handwritten form should be indelible. However, industry has long accepted that pencil is inappropriate and the FDA has repeatedly cited companies when white correction fluid was used to obliterate an incorrect entry. The proposed Part 11 revision does require that any electronic signature is electronically bound to the record.

(b) Master production and control records shall include:

(1) The name and strength of the product and a description of the dosage form;

The product name is usually the manufacturer's trade or proprietary name and where possible should be used consistently in all documentation. Dosage form refers to tablet, capsule, injection, etc. Since many pharmaceutical products are manufactured with more than one strength this should be clearly obvious in the master documentation.

(2) The name and weight or measure of each active ingredient per dosage unit or per unit of weight or measure of the drug product, and a statement of the total weight or measure of any dosage unit;

Master records usually record weights and measures of both active and inactive compounds per dosage unit for solid dosage forms such as tablets and capsules, while for liquid dosage forms percentage is more common.

(3) A complete list of components designed by names or codes sufficiently specific to indicate any special quality characteristic;

Components are usually specified by name and by an internally generated alphanumeric code. This double identification, although frequently used primarily for accounting purposes, helps to reduce the potential for usage of incorrect components—particularly if the chemical name is complex or similar to other materials. This is particularly relevant with regard to different varieties of the same component such as hydrated/anhydrous (e.g., citric acid) or crystalline/powder.

(4) An accurate statement of the weight or measure of each component, using the same weight system (metric, avoirdupois, or apothecary) for each component. Reasonable variations may be permitted, however, in the amount of components necessary for the preparation in the dosage form, provided they are justified in the master production and control records;

(5) A statement concerning any calculated excess of component;

In order to prevent errors all component weights for a product should be stated in the same system (metric, avoirdupois, or apothecary). Ideally only one unit, such as kilos or pounds, should be used throughout with a consistent policy with respect to zeros and decimal points. However, where there are significant variations, such as kilos and milligrams, the consistent use of one unit may be confusing to operators (e.g., 100 mg would be 0.0001 kilo). In these instances it may be better to use both designations, e.g., 0.0001 kilo (100 mg). There is also advantage in using the same weight system throughout a production facility to reduce the potential for misunderstanding when operators transfer between processes.

Variations from theoretical in the amount of components are permitted provided they are justified in the master records. Where variations are routine, such as a standard overage to accommodate processing losses, they should be included in the master production record so that individual calculations are not required. Other routine variations include adjustment of the amounts of components in response to assay variations. In these instances the amounts required will vary between different batches of components and it is not possible to include a standard overage in the master production record. The actual quantities are to be approved by QC, but inclusion of a “generic” calculation in the master batch record will minimize the potential for calculation error. These assay-related adjustments should not be applied to allow usage of out of specification components; batches of components that are within specification but which show atypical assay results should also not be used without adequate review and resolution of the causes of the atypical situation.

Other component variables include acids and bases used to adjust the pH of solution/suspension formulations. In these instances the actual quantity to be used is not usually included in the master documentation but is recorded in the operational batch record at the time of use. Recently some FDA reviewing chemists have been requesting that the master record indicate the maximum amount of acid and/or base that should be used. The rationale for this was reputedly to provide a warning flag if there was something atypical with the batch and to prevent frequent readjustment that could increase the level of sodium chloride in the solution (if hydrochloric acid and sodium hydroxide are used for pH adjustment). It is not known whether these concerns are based on real situations or only represent inherent FDA distrust of industry. However, there would seem to be some merit in including maximum or typical amounts as “action levels,” which, if exceeded, would require evaluation and managerial involvement.

(6) A statement of theoretical weight or measure at appropriate phases of processing;

(7) A statement of theoretical yield, including the maximum and minimum percentages of theoretical yield beyond which investigation according to §211.192 is required;

The definition of theoretical and acceptable actual yields at the main phases of processing makes it easier to evaluate and identify causes of discrepancies and to correct them. Acceptable actual yields (action levels) are calculated from historical data and, like all action levels, should be regularly reviewed and revised where appropriate. Production management personnel are usually more concerned about overall variance than individual yield variances on each batch. However, a wide range of yield variations tends to indicate that the process is not fully under control. In such cases some technical evaluation may be required to identify and correct cause of the variability.

(8) A description of the drug product containers, closures, and packaging materials, including a specimen or copy of each label and all other labeling signed and dated by the person or persons responsible for approval of such labeling;

The label is the written, printed, or graphic descriptive information placed on the product or on the immediate container. Section 502 of the Act should be consulted for the requirements for label content. Labeling is all other descriptive material, packaging for the product container, and inserts that accompany the product as a part of integrated shipment into interstate commerce (see 21 CFR 321 k and l).

In *Kordell v. U.S.* (164 F. 2d 913 and 335 U.S. 345), it was determined that labeling may have a variety of meanings. Any printed or verbal claims relating to a drug product's efficacy or use and which are available to potential customers may be defined as labeling. Labeling does not have to directly accompany the drug product in interstate commerce or be shipped simultaneously with the container. An integrated or related transaction with the function of promotion is sufficient to constitute labeling. The company must, therefore, carefully monitor all types of advertising and correspondence which may allude to the product in order to maintain control over labeling and to be in conformance with CGMP and the Act. See also [Chapter 8](#), above.

Labels and labeling copy which are authentic specimens of those used in production must be attached to the master formula. Photocopies are insufficient in this instance, since colors and paper quality are not apparent. The master batch records do not need to include advertising-related items of labeling.

Master formula labels and labeling serve as originals against which all incoming copy, designated for production, are compared prior to release. As such, they must be kept current, reflecting all changes in dosage levels, indications, contraindications, administration, warnings, and other information. The use of sequential revision number prefixes or suffixes on the basic label or labeling identification code number is strongly recommended to achieve the desired control.

Current specimens of labels and labeling which are attached to the master formula must be signed and dated by the person responsible for their approval. Most companies have a formal procedure for the approval of new and modified labeling. The review process includes several disciplines or functions, each with defined responsibilities. These usually include medical, legal, drug regulatory affairs, production, marketing, and quality assurance. It would seem unnecessary to require signatures from each of these functions on the master labeling, and usually only the person with responsibility for the overall process will sign. The records maintained by this person will, however, include the sign-off by each function.

Means for determining whether the labels and labeling being used in production exactly match the sample specimen attached to the master must be established. Alpha or numerical code designators and machine-identifying bars are two alternatives.

(9) Complete manufacturing and control instructions, sampling and testing procedures, specifications, special notations and precautions to be followed.

The master manufacturing and control records should provide sufficient detail to ensure that different, but properly trained, people will perform the process similarly. These documents are critical with respect to assuring consistent quality. If a document is too detailed it may not be read or followed; individuals may try to work from memory or establish personal informal and unapproved procedures. If insufficient detail is included there may be too much opportunity for individual judgment.

The master manufacturing records should clearly identify:

1. Name of product, product type, strength
2. Ingredients to be added: name, alphanumeric code, amounts or dosage unit or percentage
3. Amount of each ingredient for a batch
4. Sequence of adding ingredients
5. Equipment to be utilized designated by name and, where appropriate, by number
6. Processing steps with details of conditions such as time, temperature, speed
7. In-process samples, testing, acceptance criteria
8. Special precautions and hazardous conditions which exist and the necessary safety equipment to be used
9. Theoretical yields and actual yields (action levels)
10. Space for signature and date of operator/supervisor performing or checking each significant step

A second document, designed essentially on the same basis, is provided for the packaging operation (master packaging record). The master packaging record should include:

1. Name of product, product type, strength.
2. Product specifications.
3. Test methodology.
4. Sampling requirements. In-process sampling, testing, and acceptance criteria may be included in a separate SOP rather than as part of the master packaging documentation.
5. Reduced testing criteria, if appropriate.
6. Action levels beyond which QC management are to be alerted for review, comment and action.

§211.188 BATCH PRODUCTION AND CONTROL RECORDS

Batch production and control records shall be prepared for each batch of drug product produced and shall include complete information relating to the production and control of each batch.

The batch production and control record follows every production batch through the plant. It provides a detailed description of all processing operations and controls, when they are performed, by whom, and where.

Production and control operations occur at different locations within the plant. The batch records that accompany material through processing provide information for operators and also serve as a means for documenting which ingredients were added, which control measures were exercised in process and final assay of the drug product, and the huge amount of information produced during the manufacturing cycle. Because this flow of information accompanies the product through all operations, the medium of transmission must be durable and provide protection for the forms which it encloses. Since it is advisable to keep the manufacturing and packaging portions of the batch record together during these operations, many manufacturers keep batch records for a single production cycle consolidated in a polyethylene bag. In order to minimize handling and possibility of loss, laboratory records for the batch may be added just prior to release review by the control section. In addition to the information that is attached to the batch production record, the departments contributing to the manufacturing cycle must retain accurate records and comments about operations within the department.

It is insufficient if the production and control records for a released batch are correctly completed but are not available for rapid retrieval from archives. This section suggests that all completed records associated with a single batch

of production be consolidated and filed in order to ensure ready access. Since this section implies that an identifying control number be assigned to each individual batch, this number could serve as a means of indexing these record files.

There is no single correct method for assigning control or lot numbers to production batches. Many larger companies utilize a production planning function which coordinates market requirements, inventory levels, and projected manufacturing necessities. This function may assign control numbers sequentially to the batch formulas as released to production, or each product may have a block of control numbers assigned to it over a specific time period. The former method permits a general idea of when the product was manufactured; the latter indicates how many batches of a specific product have been processed. Both are compatible with the first in/first out method of inventory control.

- (a) An accurate reproduction of the appropriate master production or control record, checked for accuracy, dated, and signed:

These instructions, procedures, controls, and specifications established in the master batch formula must be duplicated to serve as a guide for the actual production operations. Accurate duplication may be achieved by copying the master by hand, mimeographing, photocopying, or computer printout methods. Copying the master for each production batch manually is generally less accurate and less economical; therefore, the last three methods are recommended. The volume of operations and equipment are the ultimate determinants.

Although the necessity for the checking of automated copying has been questioned, errors can occur when the copy is blurred, contains extraneous specks, or is partly cut off. Each page of each copy, therefore, must be checked, dated, and endorsed by an individual able to detect any error, either centrally or by a department supervisor, before manufacturing operations may commence. This may be done within each production department or by the control function by direct comparison with a verified copy of the master, or by the data processor itself if it has programming for verification.

- (b) Documentation that each significant step in the manufacture, processing, packing or holding of the batch was accomplished, including:

- (1) Dates;
- (2) Identity of individual major equipment and lines used;
- (3) Specific identification of each batch of component or in-process material used;
- (4) Weights and measures of components used in the course of processing;
- (5) In-process and laboratory control results;
- (6) Inspection of the packaging and labeling area before and after use;
- (7) A statement of the actual yield and statement of the percentage of theoretical yield at appropriate phases of processing;

- (8) Complete labeling control records, including specimens or copies of all labeling used;
- (9) Description of drug product containers and closures;
- (10) Any sampling performed;
- (11) Identification of the persons performing and directly supervising or checking each significant step in the operation;
- (12) Any investigation made according to §211.192;
- (13) Results of examinations made in accordance with §211.134.

The documentation requirements record that the steps referenced in §211.186(b)(9) have been performed. The regulations require two signatures for significant steps: that of the individual performing the step and the supervisor for confirmation. This places an important yet difficult responsibility on the supervisors. If the supervisor is actually present when the operation is performed then the signature for confirmation creates no problems. However, in real life a supervisor has many activities with several processes and people to supervise and it is not always practicable to be present when a specific operation is being performed. The supervisor must then exercise some judgment. Some examples illustrate the point.

1. To confirm that specific materials have been added to a batch it may be acceptable to check the labels from the dispensed materials. However, if confirmation is required of the weight of material added, then the supervisors would need to be present during the weighing operation.
2. To confirm that a material has been dried for a specified period of time and at a specific temperature, checking of the oven chart should be sufficient. But to confirm the pH of a solution, unless the instrument provides a printout, the supervisor would need to be present.
3. To confirm that in-process weight checks have been performed properly and at the required frequencies the supervisor may be able to rely on review of the operator data possibly coupled with an occasional weight check himself.

The need to clearly reference the specific piece of equipment used has previously been noted. In the event of a problem it may be important to identify all key parameters associated with the process stage in question: materials, process, operator, supervisor, equipment, environment. Without this information a comprehensive evaluation of the problem to identify the root cause may be unsuccessful.

Section 211.188(b)(6) requires that there shall be an inspection of the packaging and labeling area before and after use. This can be met by incorporating into the records a line clearance form which:

1. Notes the previous product packaged on the equipment.
2. Confirms that the equipment has been properly cleared of components from the previous run. If the new packaging run is the same product, then confirmation of the removal of precoded labeling components and of bulk and finished product may be adequate.
3. Confirms that all components from the previous run, except as noted in (2), have been removed from the vicinity.
4. Confirms the presence of the required components for the run about to commence.

A similar procedure is recommended for manufacturing operations. This necessity to confirm readiness for use does benefit from the availability of equipment and facility status labeling; obviously it is easier for a supervisor to sign for readiness if in addition to the check there is documentation to confirm cleaning and clearing of the previous batch of product.

The batch record must incorporate the complete labeling controls record and must contain a specimen or copy of all labels. A specimen is preferred since this gives a more accurate picture, especially with respect to color. A copy is acceptable if a specimen cannot be conveniently prepared, such as from pre-printed tubes or ampoules.

A description of drug product containers and closures should include all elements of packaging which can impact on product quality. This will include, in addition to the primary pack, closure, and label, other packaging components such as cap liners used to provide product protection for stability or as tamper evidency, secondary packaging such as cartons which carry product labeling information, tamper-evident and child-resistant features, secondary closures such as the metal coverings holding in place the elastomeric closures of vials, and also tertiary packaging such as shippers and dividers, especially where these play an important role in product protection during storage and transportation.

Subsections (12) and (13) require supervisory review, comment, and satisfactory resolution of any discrepancy or deviation from the standards prescribed. Further, any previous lot or batch of the product which might have been subjected to a similar variation from the specified procedures must be identified and reconciled before the product may be released into interstate commerce for marketing purposes. The recorded commentary should include:

1. Description of the problem.
 - a. The specific parameter that exhibits variance from the norm.
 - b. Identification of the variance: when, how, and by whom.
 - c. Potential extension to other batches of the same product or to different products.
 - d. Confirmation that the problem is real and not due to atypical reporting or analytical error.

2. Viability of rework or reprocessing of the batch and identification and approval of the method. This is to include reference to any NDA or ANDA and also the need for additional testing, inspection, or stability. Unless the rework procedure is included in the NDA/ANDA, approval from the FDA is required before the reworked product can be shipped. Also, the need for frequent reworking would tend to indicate that the production process needs to be reevaluated.
3. Identification of the root cause of the problem and initiation of appropriate corrective actions to prevent or minimize the potential for re-occurrence.
4. Appropriate supervisory or managerial review of the entire problem with signature and date.

If a single lot of bulk manufactured product is utilized in more than one packaging order, a record should exist which shows:

1. Each packaging order to which the bulk was assigned
2. Packaging control numbers
3. Quantity utilized in each order
4. Date of each packaging operation

Conversely, completion of large quantity packaging orders may require product from more than one production batch. If this condition exists, the records must list each batch used. A method must also be defined to indicate when each different production batch entered the packaging sequence and to permit accountability determinations of the total amounts used. Three systems tend to be used:

1. Separate packaging control numbers are used each time a bulk product from a different batch is introduced into the packaging program. This method segments the packaging run with two or more control numbers. The main disadvantage is that the line needs to be stopped, cleared of all bulk and finished product and precoded labeling components, and set up with the new control numbers. This can obviously result in significant disruption of packaging with consequent labor and machine utilization inefficiencies.
2. A single control number can be assigned to the entire packaging order. This obviates the problem referred to above.
3. A compromise situation may be applicable where multiple batches are involved. When a new batch of bulk product is introduced onto the packaging line, the control number is changed but the line is not cleared from the previous bulk or labeled components; these are simply allowed to be “flushed” through the line by the new batch.

The intent of the above procedures is to ensure that in the event of a recall all product involved can be identified and removed from the market expeditiously. This requires that the batch records for both manufacturing and packaging show, and cross-reference, which batch numbers were assigned to each packaging control number and which packaging control numbers were filled by bulk product from any specified batch. The first alternative described above clearly maintains a discrete correlation between individual bulk batches and individual packaging runs, thereby making any recall specific to the bulk batch or packaging run in question. The use of a single packaging control number associated with several batches of bulk product would require the recall of the entire packaging order even if only one bulk batch was suspect. The productivity benefits of this approach could outweigh the disadvantages for a production process which has been fully validated and whose performance has been confirmed by historical data. However, a further disadvantage relates to the evaluation of complaints. It would not be possible to properly evaluate a complaint on the drug product itself since there is no way to identify the specific batch of bulk product involved. The third alternative does provide a compromise. In the event of a recall it might be necessary to additionally withdraw the batches on either side of the affected batch since discrete segregation was not possible. But for complaint review most of the distributed units are identified by packaging numbers that do relate to specific bulk batches.

NUMERICAL MATERIAL IDENTIFICATION SYSTEMS

Throughout the text there are references to material identification numbers. At this point it may be useful to more fully describe a pharmaceutical alphanumeric identification system.

1. Raw material, components, and other supplies. Each material should be assigned a specific number which clearly identifies the material. Different physical or chemical forms of the material should be provided with different numbers. When package labeling text is changed, it is usual to apply a suffix to the existing number.
2. Receipts of raw materials and components. Each receipt should be allocated a sequential stock or receipt number. When more than one supplier lot is included in the receipt each lot should be given a separate number.
3. Manufacturing batch number. Each scheduled manufacturing batch should be given a sequential number. Often batches manufactured in different departments (e.g., tablets and liquids) are given a different letter prefix. Sometimes a different number, a control number, is assigned to a bulk batch after it has been released by quality assurance.

This serves as an additional check that unreleased bulk product cannot be used in the packaging cycle.

4. Product formulations are assigned unique identification, thereby allowing differentiation between products by both name and number.
5. Packaging control numbers are designated to each packaging order to provide a means of correlating packaging and bulk product and also act as the number to be used in the event of customer complaint or recalls.

§211.192 PRODUCTION RECORD REVIEW

All drug product production and control records, including those for packaging and labeling, shall be reviewed and approved by the quality control unit to determine compliance with all established, approved written procedures before a batch is released or distributed. Any unexplained discrepancy (including a percentage of theoretical yield exceeding the maximum or minimum percentages established in master production and control records) or the failure of a batch or any of its components to meet any of its specifications shall be thoroughly investigated, whether or not the batch has already been distributed. The investigation shall extend to other batches of the same drug product and other drug products that may have been associated with the specific failure or discrepancy. A written record of the investigation shall be made and shall include the conclusions and follow up.

This section requires that a product be released only after review of the entire batch record for compliance with approved written procedures. That the intent of the section has been carried out can be shown by the use of a checklist which defines the specific documents which should be in the batch record and what is to be checked on each document. If the release criteria are not stated on the batch record they should be included on the checklist. Items to be entered on the checklists would include:

1. Batch record is current and approved as an accurate copy.
2. Correct, released, components were used in manufacturing.
3. Correct quantities of components were used in manufacturing.
4. All components were within the retest dating period.
5. Manufacturing control document is properly completed.
6. Correct product was packaged.
7. Correct packaging components were used.
8. Labeling bears the correct control number, expiry date.
9. Yields and accountability are within action levels.

10. Packaging control document was properly completed.
11. Test data, in-process, and control laboratory are within specifications.
12. Retained samples have been taken.
13. Written investigation of any deviation from procedure, with any approvals and data to support remedial action.

A full and comprehensive review of every aspect of the manufacturing, packaging, and control documentation is very time consuming and rarely identifies more than the absence of signatures or the misplacement of a document. Consequently, the emphasis must be on the operations themselves, ensuring that all employees understand the importance of the procedures and the need to follow them or document atypical or noncomplying situations; and that supervisors and managers pay enough attention to this during their routine activities.

When production deviations occur they must be documented, investigated, and appropriate levels of management must be involved in the review of the data and in any decision making. It is particularly important to decide what actions are required to minimize the potential for reoccurrence—retraining, process improvement, revalidation.

§211.194 LABORATORY RECORDS

(a) Laboratory records shall include complete data derived from all tests necessary to assure compliance with established specifications and standards, including examinations and assays, as follows:

(1) A description of the sample received for testing with identification of source (that is, location from where sample was obtained), quantity, lot number or other distinctive code, date sample was taken, and date sample was received for testing.

The description of the sample simply requires that there be an adequate identification, such as the name or identification code of the material; it does not mean visual appearance. The lot number specific to the material sampled must also be noted.

Where samples are taken from a representative number of containers it is necessary to cross-reference the samples to the containers from which they were taken. In the event of any query it is then possible to precisely pinpoint the sample source.

The amount of sample taken needs to be recorded to allow effective reconciliation. For materials in bulk (raw materials, granules, tablets) it may not be necessary to actually weigh or measure each sample. The use of sampling equipment or sample containers which have been “roughly calibrated” may provide data of sufficient accuracy.

The need to record the date of sampling and the date of receipt for testing seems to be of no value. Recording the sampling date is useful since some materials may undergo change, such as moisture pick-up, between sampling and testing. The date of receipt for testing would seem to have little relevance. However, most QC departments do record the date of sample receipt as part of the managerial evaluation of laboratory effectiveness.

(2) A statement of each method used in the testing of the sample. The statement shall indicate the locations of data that establish that the methods used in the testing of the sample meet proper standards of accuracy and reliability as applied to the product tested. (If the method employed is in the current revision of the United States Pharmacopeia, National Formulary, Association of Official Analytical Chemists, Book of Methods, or in other recognized standard references, or is detailed in an approved new drug application and the referenced method is not modified, a statement indicating the method and reference will suffice.) The suitability of all testing methods used shall be verified under actual conditions of use.

Test methodology may be modified with time and it is important that the retained records clearly indicate which methodology was actually used. This is usually done by indicating the monograph reference number or issue date. Obviously copies of superceded monographs that relate the retained records must be retained.

Analytical methodology must be validated and the validation data must be retained. As written the regulations would require that for each method used the records for each sample tested should reference the location of the validation data. This would seem to be onerous and unnecessary provided the monograph, or some other procedure, indicates the location. It is assumed that “official” methods have been validated and reference to the official source is considered to be adequate. However, for both official methods and for methods validated in another laboratory it is necessary to verify suitability in the individual laboratory [§211.165(e)]. The degree of work to verify suitability may vary with the complexity of the method. It may be sufficient to perform the method with samples of known composition or that have previously been analyzed.

(3) A statement of the weight or measure of sample used for each test where appropriate.

(4) A complete record of all data secured in the course of each test, including all graphs, charts, and spectra from laboratory instrumentation properly identified to show the specific component, drug product container, closure, in-process material, or drug product, and lot tested.

It is difficult to understand why it was necessary to specify the recording of “weight or measure . . . where appropriate” since without such data it would not be possible to evaluate quantitative results. The retention of raw data does

bulk-up the size of batch records. However, their retention does allow reevaluation in the event of a future query.

The requirement for a “complete record of all data secured in the course of each test” took on new emphasis when the FDA identified that some companies were reporting only “good” results in submissions. All results must be reported (see also §211.165) and any out-of-specification results fully evaluated and explained.

(5) A record of all calculations performed in connection with the test, including units of measure, conversion factors, and equivalency factors.

(6) A statement of the results of tests and how the results compare with established standards of identity, strength, quality, and purity for the component, drug product container, closure, in-process material, or drug product tested.

As indicated earlier (§211.68), the use of automatic calculation procedures is acceptable; in fact these are preferable since they minimize the potential for individual random calculation errors.

The results obtained from testing must be compared with “established standards.” It is common practice to establish action levels based on historical data. Confirmation that results lie within the action levels may be delegated to a responsible analyst. Results outside of the action level, but inside specification, are usually referred to a more senior individual and require evaluation for possible cause before making a decision on status. The written methodology or procedures should clearly identify these action levels and the review process.

(7) The initials or signature of the person who performs each test and the date(s) the tests were performed.

(8) The initials or signature of a second person showing that the original records have been reviewed for accuracy, completeness, and compliance with established standards.

Records must indicate who performed each test. Either initials or signature are considered adequate. Since the initials and signatures of many people are indecipherable, it is recommended that printed or typed names should also be shown. Alternatively, a master record could be maintained of all departmental initials and signatures. This approach would have benefit anywhere in the production process where signatures or initials are required.

The depth of checking necessary to confirm the accuracy and completeness of the records will vary with the degrees of automation and complexity in the procedures. However, replacement of routine checking by random or periodic audit is not acceptable.

(b) Complete records shall be maintained of any modification of an established method employed in testing. Such records shall include the reason for

the modification and data to verify that the modification produced results that are at least as accurate and reliable for the material being tested as the established method.

It is important to remember that the applicability of test data is dependent on confirmation of the validity of the methodology. Because of the work involved in validating a modified method, it is desirable to make changes only when essential.

(c) Complete records shall be maintained of any testing and standardization of laboratory reference standards, reagents, and standard solutions.

(d) Complete records shall be maintained of the periodic calibration of laboratory instruments, apparatus, gauges, and recording devices required by §211.160(b)(4).

(e) Complete records shall be maintained of all stability testing performed in accordance with §211.166.

Standardized reagents and reference standards play key roles in analytical methodology. Procedures must define how standardization is to be performed, the frequency of restandardization, and the operational limits. These limits will identify the required degree of precision between replicate results and also the maximum allowable values from nominal. If individual values vary too much from nominal, revalidation may be necessary. Where secondary reference standards are used their suitability must be confirmed by cross-calibration with a defined primary standard.

The subjects of calibration and stability have been addressed previously in §211.160(b)(4) and §211.166, respectively.

§211.196 DISTRIBUTION RECORDS

Distribution records shall contain the name and strength of the product and description of the dosage form, name and address of the consignee, date and quantity shipped, and lot or control number of the drug product. For compressed medical gas products, distribution records are not required to contain lot or control numbers.

The primary purpose of this section is to ensure that adequate data are available to access trade customers should a recall be initiated. The recording of lot number to each order will certainly accomplish this purpose; other approaches can achieve the same result. The recording of dates on which a specific lot of product commenced and ceased distribution may be used. All customers receiving the product between these dates could then be contacted. Obviously on the first and last days of distribution, some of the customers may have received product from the end of the previous lot or the beginning of the next lot. This overlap should in no way adversely impact on the effectiveness of a recall.

Whatever system is used, it must accommodate the reintroduction of returned goods into the distribution chain.

Distribution records include a wide range of documentation such as invoices, bills of lading, customers' receipts, and internal warehouse storage and inventory records. The information required need not be on every document. Also customer codes and product codes may be used as alternates to customer names and addresses and product names.

Compendial articles are to be in compliance with the current compendium when shipped. This can create some difficulties with respect to inventories of components, labeling or products when there are compendial changes. Compliance Policy Guide 7132.02 does suggest that regulatory action should not be taken if a company is using up existing stock of labels in a reasonable time and that the product or material is otherwise in compliance with the new monograph.

§211.198 COMPLAINT FILES

(a) Written procedures describing the handling of all written and oral complaints regarding a drug product shall be established and followed. Such procedures shall include provisions for review by the quality control unit, of any complaint involving the possible failure of a drug product to meet any of its specifications and, for such drug products, a determination as to the need for an investigation in accordance with §211.192. Such procedures shall include provisions for review to determine whether the complaint represents a serious and unexpected adverse drug experience which is required to be reported to the Food and Drug Administration in accordance with §310.305 of this chapter.

(b) A written record of each complaint shall be maintained in a file designated for drug product complaints. The file regarding such drug product complaints shall be maintained at the establishment where the drug product involved was manufactured, processed, or packed, or such file may be maintained at another facility if the written records in such files are readily available for inspection at that other facility. Written records involving a drug product shall be maintained until at least 1 year after the expiration date of the drug product, or 1 year after the date that the complaint was received, whichever is longer. In the case of certain OTC drug products lacking expiration dating because they meet the criteria for exemption under §211.137, such written records shall be maintained for 3 years after distribution of the drug product.

(1) The written record shall include the following information, where known: the name and strength of the drug product, lot number, name of complaint, and reply to complainant.

(2) Where an investigation under §211.192 is conducted, the written record shall include the findings of the investigation and follow up. The rec-

ord or copy of the record of the investigation shall be maintained at the establishment where the investigation occurred in accordance with §211.180(c).

(3) Where an investigation under §211.192 is not conducted, the written record shall include the reason that an investigation was found not to be necessary and the name of the responsible person making such a determination.

Complaints received from consumers, professionals, and the trade serve as a primary means of obtaining feedback about product quality after distribution. It is necessary, therefore, that each complaint or inquiry be evaluated by knowledgeable and responsible personnel.

The records of production, packaging, and distribution of drug and the retained samples provide the basis for assessing the validity and seriousness of the alleged deviations that precipitated the complaint. It is important, therefore, that the records for each production lot are readily available. The complaint file itself also plays an important role in determining whether any other similar complaints have been received on the lot in question, or on any other lots of the same product.

The evaluation of complaints serves several valuable purposes. First, there is the urgent need to confirm whether consumers are potentially at risk and to initiate any appropriate action. A second value is the review of the product and its production process to establish whether any modifications are required. Third is the need to rapidly respond to the customer, thereby attempting to maintain confidence in the product and company.

Various surveys have shown that only a proportion of those people receiving substandard product will actually complain. This needs to be remembered when evaluating the extent of a problem. Some companies have attempted to increase the amount of feedback, in order to gain more information, by making it easier for the consumer to contact the company. The use of toll-free telephone numbers on products has been successful. A secondary benefit arising from such approaches has been an increase in the number of positive suggestions for improvements from consumers.

It should be noted that for NDA and ANDA products the FDA requires a "field alert report" to be submitted within three days of a company being made aware of any mislabeling, bacterial contamination, any significant deterioration or failure to meet the registered specifications for a distributed product (§314.81).

This section does not address specific adverse drug reactions. However, reports of adverse drug reactions, if considered atypical with respect to the reaction itself or the frequency, will also require evaluation of the product.

The recording of complaint data should allow examination by product, by lot number, by complaint type, and by pack type and size. This data, along with sales volumes, makes it possible to pinpoint the source of the problem and to monitor trends.

Although complaint data provide useful quality data, this must not be seen as an end in itself. Where complaints continue it may be worth considering a field evaluation of the product to obtain more extensive information on the potential problem.

This section must also be considered in the context of drug products liability where it has served as a fertile field for exploration by plaintiffs' lawyers. It is, therefore, another instance of where occasional, or as-needed, review in house, by internal local counsel, should be undertaken.

EXAMPLES OF OBSERVATIONS FROM FDA 483 CITATIONS

1. Theoretical yields and actual yields are not determined for every batch.
2. The firm's written procedures for the investigation of complaints is inadequate and simply states that the complaint file is maintained at corporate headquarters. Complaint investigations that are conducted do not include written justification of why the investigation did not extend to other lots that could have been affected or why increased sampling of the affected lot was not done.
3. The Annual Product Review for . . . Capsules is inadequate in that it only consists of a table listing lots manufactured during the year and content uniformity values for ten capsules in each lot. No additional information is contained in the report.
4. Retain samples. Forty-three defective products were found in the annual reviews of retain samples. There was no follow-up to any of these product defects. There are no retain samples for fifty-eight lots manufactured during the year.

SUGGESTED READINGS

1. FDA Center for Drug Evaluation and Research, Guidance for Industry. Format and Content for the CMC Section of an Annual Report, September 1994.
2. FDA, Electronic Signatures; Electronic Records, *Fed. Reg.*, 59(168), 45160, 1994.
3. Barr Laboratories, Inc., Refusal to Approve Certain Abbreviated Applications; Opportunity for a Hearing, *Fed. Reg.*, 58(102), 31035, 1993.
4. *United States of America, Plaintiff, v. Barr Laboratories, Inc., et al., Defendants*. No. CIV A 92-1744. United States District Court, D. New Jersey, February 5, 1993.
5. M. R. Frank, Accuracy in FDA Submissions: A Laudable Goal with Significant Legal Implications, *Food and Drug Law J.*, 47, 677, 1993.
6. Sidney H. Willig, Impact of Drug Products Liability on Needs for Pharmacoepidemiology.

- logic Studies and Expertise (Chaper 4 in *Pharmacoepidemiology*, edited by S. A. Edlavitch, vol. 1, Lewis Publishers Inc.), 1989.
7. James R. Ruger and Sidney H. Willig, A View from the U.S. Court Room Chapter 8 in *Pharmacoepidemiology*, edited by B. L. Strom, U. of Pa. Health System, 1999. 3rd edition.
 8. S. H. Willig, Address to 3rd International Congress on Pharmacoepidemiology. University of Minnesota, September 1987.

Following study of this chapter, it might be helpful for staff review to discuss specific guides provided by the FDA to their field staff and others, that are pertinent as Regulatory Action Guidance.

Sec. 470.100 Orders for Post-Approval Record Reviews (CPG 7132c.07)

BACKGROUND:

This document states the Food and Drug Administration's policy and procedures for the issuance of orders to conduct record reviews for approved new drug products for human and animal use.

During the generic drug investigations the agency encountered some problems that could not be addressed with traditional legal tools. One such problem involved situations where omissions, inconsistencies, untrue statements of material facts, or outright fraud were found in records (e.g., biobatch manufacturing records) submitted as part of some ANDAs (for human use). Another problem involved departures from approved manufacturing procedures. In these instances, where only a few applications are implicated, FDA can readily initiate action against specific products found to have been approved on the basis of false or incomplete information, or which are not made in accordance with approved procedures. However, where many applications are implicated, the sheer volume of records which must be reviewed makes it difficult to determine how many products are involved.

In the 1989 generic drug cases, the affected firms cooperated by engaging qualified outside consultants to review all records, and report results to FDA. Absent such voluntary cooperation, the agency may have to issue orders requiring firms to conduct such reviews.

The agency has concluded that it has a legal basis for requiring drug manufacturers to conduct and report post-approval record reviews under authority of Sections 505(k), 505(e), 512(e), 512(l), 512(m)(4), 512(m)(5), 701(a), 704(a) of the Federal Food, Drug, and Cosmetic Act (the Act) and the Current Good Manufacturing Practice Regulations for drugs that are enforceable under Section 501(a)(2)(B) of the Act. Sections 505(k), 512(l), and 512(m) of the Act sanction such orders on the basis of a finding that such records and reports are necessary in order to determine, or facilitate a determination, whether there is or may be ground for invoking Sections 505(e), 512(e), and/or 512(m)(4).

POLICY:

The FDA may issue an order, requiring a records review and report, where there are questions about the safety or effectiveness of an approved drug, or about the truth or falsity of information submitted in support of the original application, in order to determine whether or not such questions are serious enough to warrant withdrawal of the application approval. Such questions may arise, for example, from findings of noncompliance with approved manufacturing procedures, untrue statements of material facts, fraud, or application omissions and inconsistencies. Such orders shall afford the applicant an opportunity to respond informally to the basis for the order.

REGULATORY ACTION GUIDANCE:

Recommendations for a post-approval record review order may be made by field district offices or scientific review divisions in accordance with the above policy.

12

Returned and Salvaged Drug Products (Subpart K)

§211.204 RETURNED DRUG PRODUCTS

Returned drug products shall be identified as such and held. If the conditions under which returned drug products have been held, stored, or shipped before or during their return, or if the condition of the drug product, its container, carton, or labeling, as a result of storage or shipping, casts doubt on the safety, identity, strength, quality, or purity of the drug product, the returned drug product shall be destroyed unless examination, testing, or other investigations prove the drug product meets appropriate standards of safety, identity, strength, quality, or purity. A drug product may be reprocessed provided the subsequent drug product meets appropriate standards, specifications, and characteristics. Records of returned drug products shall be maintained and shall include the name and label potency of the drug product dosage form, lot number (or control number or batch number), reason for return, quantity returned, date of disposition, and ultimate disposition of the returned drug product. If the reason for a drug product being returned implicates associated batches, an appropriate investigation shall be conducted in accordance with the requirements of §211.192. Procedures for holding, testing, and reprocessing of returned drug products shall be in writing and shall be followed.

The intent of this section is:

1. To provoke an examination of the reasons for return in order to decide whether further action is required on the lot, on related lots, or to the storage and distribution chain.

If the goods are known to have been handled within the normal range of conditions in the distribution chain, it may be adequate to redistribute after visual examination.

Where the distribution or storage conditions are unknown or have been extreme, then return to stock, as is or after reprocessing, can only be considered after appropriate evaluation which confirms no unacceptable deterioration.

2. To maintain full and comprehensive records to allow identification of returned goods distribution and accountability in the event of a recall. This places a considerable burden of work on those responsible for distribution since returns from the trade can be considerable—incorrect deliveries, ordered in excess, damaged in transit, nearing the end of shelf-life. The regulations require recording of the product details and disposition of returns and also the reason for the return.

3. To remove from commerce portions of a lot which may have been adversely affected by atypical distribution conditions (see also §211.208).

§211.208 DRUG PRODUCT SALVAGING

Drug products that have been subjected to improper storage conditions including extremes in temperature, humidity, smoke, fumes, pressure, age, or radiation due to natural disasters, fires, accidents, or equipment failures shall not be salvaged and returned to the marketplace. Whenever there is a question whether drug products have been subjected to such conditions, salvaging operations may be conducted only if there is (a) evidence from laboratory tests and assays (including animal feeding studies where applicable) that the drug products meet all applicable standards of identity, strength, quality, and purity and (b) evidence from inspection of the premises that the drug products and their associated packaging were not subjected to improper storage conditions as a result of the disaster or accident. Organoleptic examinations shall be acceptable only as supplemental evidence that the drug products meet appropriate standards of identity, strength, quality, and purity. Records including name, lot number, and disposition shall be maintained for drug products subject to this section.

This section clearly states that products that have been exposed to improper storage conditions “shall not be salvaged and returned to the marketplace.” As is the case of all agency rules and regulations, the word “shall” is mandatory while the word “may” is discretionary. However, this does not mean, for example, that in the event of a warehouse fire all goods stored there must be destroyed. If it is possible that some of the goods may not have been exposed to adverse conditions during the fire, then it is acceptable to evaluate these products, and if they do fully comply with the appropriate standards, they may be suitable for salvage.

EXAMPLES OF OBSERVATIONS FROM FDA 483 CITATIONS

1. Reason for product return not documented.
2. No evaluation of the cause of the returned “bad tablets.”
3. No validation of reprocessing of tablets from compression machine set up.

Following study of this chapter, it might be helpful for staff review, to discuss specific guides provided by the FDA to their field staff and others, that are pertinent as Regulatory Action Guidance.

Sec. 160.750 Drug and Device Products (Including Biologics and Animal Drugs) Found in Violation of GMPRs—Reconditioning (CPG 7153.14)

BACKGROUND:

The question has arisen as to whether drug and device products that have been produced or held by methods or under conditions not in accordance with Good Manufacturing Practice regulations, and consequently determined to be adulterated, may be reconditioned and returned to trade channels. Situations covered by this CPG are those in which a “formal” judgment of adulteration has been rendered; e.g., drug and device products that have been seized and condemned pursuant to Section 304 of the Act due to Good Manufacturing Practice deficiencies, drug and device products that have been recalled because they were found to be in violation of the CGMPRs, etc. Although GMP deficiencies can be corrected in subsequent batches or lots of the involved product(s), it may be difficult or impossible to correct the effect of the deficiencies retrospectively in batches or lots already produced.

POLICY:

The reconditioning of drug and device products found to be adulterated as a result of having been produced, processed, or held under conditions which are deficient with regard to Good Manufacturing Practice regulations may be approved providing all of the following conditions are met as follows:

1. Any reconditioning proposal must be reviewed by all parties concerned (District, Center, OE, * OCC *) to determine whether the plan can reasonably be expected to bring the drug device products(s) into compliance.
2. In order to be acceptable, a proposed reconditioning plan must overcome any observed GMP deficiencies and correct any known product defects present.
3. If the lot to be reconditioned is held within the facility where the GMP violations occurred, the violative conditions must be corrected in advance of accepting a reconditioning proposal, or included as part of the reconditioning proposal.

4. If the lot is held in a facility separate from the one in which the GMP violations occurred and the separate facility is in compliance, a reconditioning proposal can be considered as provided for in paragraphs 1 and 2 above.

No product shall be released until all reconditioning commitments are fully met as verified by FDA.

* Material between asterisks is new or revised *

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Sec. 300.200 Reconditioners/Rebuilders of Medical Devices (CPG 7124.28)

BACKGROUND:

An increasing number of firms are acquiring previously owned medical devices and reconditioning/rebuilding these devices for resale. FDA has received inquiries about the application of the Federal Food, Drug, and Cosmetic Act (FFDCA) and its implementing regulations to these firms.

POLICY:

A reconditioner/rebuilder is a person or firm that *acquires ownership* of used medical devices and restores and/or refurbishes these to the device manufacturer's original or current specifications, or new specifications, *for purposes of resale or commercial distribution*. (A person or firm that services, repairs, or reconditions a medical device and returns the device to its owner is *not* covered by this guide.)

This guide applies to reconditioners/rebuilders of medical devices, as defined by section 201(h) of the FFDCA, including radiation-emitting devices and major components of diagnostic x-ray systems listed under 21 CFR 1020.30(a)(1), *except* for the following persons or firms:

Assemblers of X-Ray Equipment Who Incidentally Reload Diagnostic X-Ray Tube Assemblies

The scope of the FDA policy regarding the exemption of diagnostic x-ray assemblers that reload x-ray tube housing assemblers from this guide is found in CPG 7133.20 (See Sec. 389.700), "Reloaders of X-Ray Tube Housing Assemblies; Medical Device Registration, Device Listing, and Biennial Inspection" (11/01/81).

The May 28, 1976, Medical Device Amendments to the FFDCA and the implementing regulations apply to reconditioners/rebuilders as follows:

A. REGISTRATION

Reconditioners/rebuilders of medical devices intended for human use must register with FDA as set forth under section 510 of the FFDCA and 21 CFR 807.20(a).

B. PREMARKET NOTIFICATION

Reconditioners/rebuilders are subject to the premarket notification requirements of 21 CFR 807.81. If the original manufacturer performs the reconditioning/rebuilding, a 510(k) must be submitted only if required by 21 CFR 807.81(a)(3).

C. LABELING

1. In accordance with 21 CFR 801.1 reconditioners/rebuilders of medical devices must clearly and conspicuously disclose on the device's label the following:
 - a. The name and place of business of the person or firm that rebuilt or reconditioned the device.
 - b. The name and business address of the original manufacturer, distributor, or packer of the device, if different from 1.a. above, where that manufacturer's, distributor's, or packer's original or current (where applicable) specifications are used.
 - c. See 21 CFR 801.109 give reconditioner's (rebuilder's) name.
 - d. Subject to GMP/21 CFR 820.
 - e. Subject to MDR 21 CFR 803 (3/95).

Sec. 448.100 Reconditioning of New Drugs Which Do Not Have Approved NDAs/ANDAs CPG (7132c.03)

BACKGROUND:

Prior policy under the DESI program permitted the marketing of new drugs evaluated as effective upon the submission of a New Drug Application (NDA) or Abbreviated New Drug Application (ANDA). This policy was challenged and overturned in a decision handed down on July 29, 1975, by the U.S. District Court for the District of Columbia (Hoffman La Roche vs. Caspar Weinberger, et al). The Agency implemented this order (Judge Green's decision) through Compliance Program 7332.26 covering products identical or related ("me too" drugs) to DESI drugs identified in a list published 1/76 (DHEW publication No. (FDA) 76-3009).

Agency policy as set forth in the program required that such new drugs be discontinued from marketing and recalled if substantial stocks remain in trade channels. When responsible firms have failed to initiate the above actions after being warned by issuance of a * warning letter *, unapproved new drugs have been seized.

Although recall or seizure may have been necessary for uniform enforcement and protection of the public health, destruction of such recalled or seized material is not always required provided adequate safeguards are taken.

POLICY:

In those instances in which an Abbreviated New Drug Application has been submitted and is currently pending, we will not insist upon destruction of recalled or seized material resulting from implementation of Compliance Policy Guide 7132c.02 involving DESI effective drugs provided:

1. Recalled stocks are quarantined by the formulator and not held by consignees, i.e., substantial stocks in the hands of consignees must be disposed of either by return to the formulator or by destruction. Failure to do so will result in recommendation for regulatory action by the district, preferably seizure.
2. Recalled (quarantined lots at the formulator) or seized material may not be released until and unless all the following conditions are met:
 - A. Approval of an NDA or ANDA is received.
 - B. The firm can validate that the lots in question were manufactured in accordance with the specifications of the approved NDA/ANDA including the following:
 1. Compliance with CGMP.
 2. Affected lots meet all purity, potency, and labeling standards specified by the approved NDA/ANDA.

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Repacking and Relabeling

The terms “repacking” and “relabeling” are commonly used to describe operations in which a drug product obtained from a manufacturer is packaged and labeled for distribution to a wholesaler or to a retail outlet. The repacking and relabeling operations are little different from the operations of the manufacturer who has drug product in bulk storage and packages and labels it in the final market container. The major difference is that the manufacturer has had control of the components and in-process material and, therefore, generally has more information about the quality and storage conditions of the drug product than the repacker. Additionally, the drug product has not been exposed to the hazards of transport by common carrier.

It seems important, therefore, that the repacker make special efforts to be assured of the quality of the product being repacked. There are three major areas of concern:

1. Identity: Is the product what it purports to be?
2. Strength or potency: What has happened to the drug product during transportation and bulk storage, both at the point of manufacture and at the repacker? Frequently, stability data for bulk storage are lacking. Expiration dates provided by the manufacturer for the drug product in the final market container are not applicable to material in fiber drums. In the usual repacking operation, moreover, a drum may be opened

several times before its contents are exhausted. Expiration dates apply only to unopened containers.

3. Expiration date: What is the proper method for setting an expiration date for a product that has been held for some time in one type of container, which may have been opened, and is now repacked in a different type of container?

The typical repacker who has little in-house laboratory capability has difficulty in addressing any of the three concerns.

The FDA believes that a repacker should exercise control over incoming drug products for repacking and relabeling as is required for components in the CGMP regulations, essentially reading “drug product” for “component” throughout Subpart E, §211.86, 211.87, and 211.89. Since the regulations specifically apply to components and not to drug products [defined in §210.3(b)(4), “drug product” means a finished dosage form, for example, tablet, capsule, solution, and so forth, that contains an active drug ingredient generally, but not necessarily, in association with inactive ingredients] clearly distinguished from components [defined in §210.3(b)(3), “component” means any ingredient intended for use in the manufacture of a drug product], the FDA justifies its position by pointing out that repacking and relabeling operations are subsumed in the term “production” and also in the terms “packaging” and “labeling.”

Whether the courts will uphold the FDA interpretation of the regulations is yet to be seen, and the situation may not be directly resolved. Under §210.1 the CGMP regulations are “the minimum current good manufacturing practice” to assure drug quality. It is expected that the FDA will hold that even if the practices are not mandated by the regulations and even if the practices are not current with repackers, it is “good manufacturing practice” for repackers to treat drug products for repacking and relabeling as if they were components.

Whether a practice is “good” would seem to depend upon the exact circumstances. A cost–benefit decision must be made for each practice in its total setting as to whether the additional assurance of the drug quality afforded by the practice is worth the additional cost. Laboratory procedures that impose a trifling cost on manufacturers who already have laboratory facilities impose large direct and indirect costs on repackers who use consulting laboratories or impose capital costs for the equipping and staffing of an in-house laboratory. Since repackers may have new needs for disclosure on product labels under 21 CFR 201.1, the problem is met head-on in the identification of material to be repacked. In the past the FDA seems to have held that nonchemical identity testing is acceptable for domestically produced products; that is, visual comparison of the drug product with an authenticated (by the manufacturer) sample of the drug product is acceptable *if there is little similarity between different drug products handled*. It is unclear whether “little similarity” applies to the repacker, the original manufac-

turer, or both. If the drug product is received from a foreign manufacturer, a chemical or physical identity test of each active ingredient in the drug product is required.

It is difficult to see why a dual standard is needed, since both domestic and foreign suppliers of drug products must comply with CGMP regulations. Because of the physical similarity of many products, it seems reasonable to require a specific identity test for each active ingredient in a drug product to be repacked or relabeled. (The “little similarity” test can be checked by choosing a dosage unit present in a repacking plant and checking to see if it can be unequivocally identified by visual inspection alone.) Whether this seemingly reasonable requirement is also good is more difficult to decide. Obviously, a misidentified drug product will be mislabeled and will usually be a hazard to health. Since it is the clear intent of Congress that adulterated or mislabeled drug product not reach the marketplace, it is necessary to determine if visual examination for identity has ever led to the *production* (not *distribution*, since if a product exists, there is the probability that it will be distributed) of mislabeled drug product; that is, it should be determined if current practice is adequate to safeguard public health or whether good (better) practice should be required.

If the FDA should enforce a specific identity test for each active ingredient in a drug product to be repacked or relabeled, the intent to do so should be made explicit. The economic impact of such a requirement should be determined on repackers, since repackers generally do not have in-house laboratory facilities, repack a large number of different products, and compete primarily on the basis of low price. This economic study will be complicated by the existence of repackers who also do some manufacturing of drug products and, thus, already have minimal laboratory facilities and personnel. Because of the economic impact, it is obvious that enforcement of the requirement should be simultaneous for all repackers.

The problems of stability and expiration dating also must be faced by repackers who receive drug product in packages different from the final container-closure system or who repeatedly package from the same bulk container. If a manufacturer suggests a period of time in which the drug product packed in a particular container-closure system will meet all its quality specifications, what can be said about the product stored in bulk? How is an expected decline in product strength in bulk storage to be related to a specific expiration date on the final container? What happens to product quality if the bulk container is opened repeatedly for repackaging?

In the strictest sense, the questions can be answered only by assay of the drug product for active ingredients immediately before repacking and a knowledge of the decomposition rate under ambient conditions in the final container-closure system. Since adsorption of moisture may affect stability of components in uncoated tablets, it is not safe to assume that a manufacturer’s expiration date

for bulk is satisfactory even for drug product packed in a more protective container-closure system, because moisture may be added to the tablet either due to repeated opening of the bulk container or by packaging at a higher relative humidity than that in which the tablets were manufactured. Again the lack of in-house laboratory facilities works against the repacker's having sufficient data and expertise to give an informed answer to the questions.

A temporary expedient might be to use on the repacked product an expiration date *from the time of manufacture*, based on stress tests in the final container-closure system (but not to exceed 2 years) and to follow the actual product decomposition at ambient conditions. The dependency on moisture content should be determined and, with sufficient experience, some estimate of decomposition during bulk storage should be able to be made.

Another area of concern is drug product labeling. A repacker customarily prepares labels to match information on the label of the bulk container, a label supplied by the manufacturer, or a label supplied by the buyer. There is generally no independent label review to assure compliance with the regulations in 21 CFR Part 201—Labeling, §330.1(g) and Part 369—Interpretive Statements Re Warnings, and specific labeling requirements for classes of products for which monographs have been established (such as antacids, emetics, and daytime sedatives). If there is any error in the manufacturer's label, or more frequently, if there have been mandatory label changes (such as change in the official title of a component) between the time of bulk packaging and the time of relabeling, the final product will probably be mislabeled. This occurs because repackers generally do not make an independent check as to whether label copy is correct at the time of relabeling, and they do not have personnel who are aware of the need for such a check or the location of the pertinent information.

The repacker who is also a wholesaler has a problem with regard to distribution records. Distribution records are required by Section 211.196 to contain the name and strength of the product and a description of the dosage form, name and address of the consignee, date and quantity shipped, and lot or control number of the drug product. Wholesaler invoices, however, customarily do not have a description of the dosage form and do not have the lot or control number of the item shipped. Since the invoice usually has the item identification number from which the description of the dosage form can be obtained or the name of the product itself is a description of the dosage form, it can be reasonably argued that the distribution records do contain this bit of information. However, there is no arguing that a recorded lot number does not follow the drug product from wholesaler to retail distributor.

The reasons for this lack is easy to understand. Drug products shipped by wholesalers are frequently returned and reshipped. Keeping track of this would produce a cumbersome, expensive system of doubtful reliability. The problem is the number of accounts serviced by wholesalers as compared with the number

of direct-to-retailer accounts serviced by manufacturers, and the small number of units of a given item in a single shipment to these accounts. A repacker-wholesaler generally will not have a record of the lot numbers of items distributed to individual retail accounts.

Clarification of the regulations is obviously necessary. An equitable interpretation might be that lot numbers are required to be recorded for products shipped by a manufacturer to repackers, wholesalers, or direct-to-retailer accounts and that repacker-wholesalers record lot numbers through the transfer of the repacked-relabeled drug product to the wholesale warehouse for retail distribution. This would give the same records for a drug product as are currently available when a manufacture ships to a wholesaler who later distributes to a retailer.

The lack of lot number on wholesaler invoices should not substantially affect ability to recall. Wholesalers customarily send recall notices to all accounts, or all accounts that purchased product after the date on which the specific lot was placed in retail distribution, or the manufacturer notifies all pharmacies in the area in which the lot was distributed.

Another area of concern relates to the usual lack of in-house laboratory facilities. Assuming that product specifications have been written and that the certificate of analysis provided by the manufacturer has been properly prepared, signed, and dated, validation of the certificate is required. This entails sending a sample to a consulting laboratory for analysis and comparison of the analysis by the consulting laboratory with the certificate of analysis from the manufacturer. Results will rarely be identical. Criteria for agreement between the two must be present in order to decide whether the certificate from the manufacturer is valid. If there is no in-house laboratory, there is probably no one sufficiently knowledgeable in analytical methodology to have an informed opinion of what degree of agreement constitutes validation. A knowledgeable consultant must then be employed.

If a consulting laboratory is used to provide analyses or stability studies not obtainable from the manufacturer, the problem of the validation of the results of the consulting laboratory arises, and, thus, a second consulting laboratory must be used. If there is lack of agreement, a third or even fourth laboratory may be involved. It is suggested that initially all certificates have been shown to be valid, and thereafter not less than every fourth certificate should be validated.

Other areas of importance to repackers are standard operating procedures, documentation of formal training in CGMP for all employees in the repacking-relabeling operations, and process validation (accuracy of label and labeling counters, fill accuracy, change in weight of tablets due to abrasion in packaging and its effect on compliance with weight variation requirements).

The standard operating procedures manual might contain the following sections:

1. Composition and scope of the quality control unit
2. Statement of laboratory facilities
3. How specifications are written, reviewed, and approved
 - a. Components
 - b. Drug products
 - c. Containers
 - d. Closures
 - e. Packaging materials
 - f. Labeling
 - g. Job descriptions
4. Job descriptions, including consultants
5. Training in CGMP: employees, frequency
6. Protective clothing
7. Limited access areas: who is permitted to enter
8. Health check as per 21 CFR 211.28
9. Lighting description
10. Ventilating description
11. Proof of potable water (analysis of water supply)
12. Trash disposal (contract for removal)
13. Washing facilities as per 21 CFR 211.52 (add “toilet paper” and “container for used towels”)
14. Sanitation program (contract with cleaners and exterminators)
15. Maintenance program (inside and out)
16. Equipment cleaning directions (including disassembly and reassembly)
17. Calibration of mechanical equipment
18. Controls on computer records
19. Receiving directions
20. Sampling directions
21. Testing specifications
22. Conditions for acceptance, reexamination, rejection
23. Assurance of first in/first out
24. Disposal of rejected materials
25. Validation of processes
26. Validation of supplier testing
27. Mechanisms for investigation and correction of deviations
28. Reprocessing procedures
29. Special procedures for gang printing of labels
30. Procedures for reconciliation of labeling
31. Procedures to prevent contamination of drug product
32. Procedures for packing and labeling
33. Setting of expiration dates: stability testing program

34. Directions for warehousing
35. Records review
36. Returned drug products
37. Complaints
38. Recall procedures

Although superficial consideration of repackaging–relabeling might indicate that these operations have little effect on product quality, the more thorough examination listed above of what is involved in the operations and the probable impact on product safety and efficacy shows that repackaging–relabeling is a critical operation that requires all of the safeguards of an adequate quality control unit.

The FDA established the following policy for repackaging of drug products into unit dose containers.

Policy: No action will be initiated against any repackaging firm, including shared services, or drug product in a unit dose container meeting all other conditions of FDA's repackaging requirements solely on the basis of the failure of the repackaging firm to have stability studies supporting the expiration dates used, provided:

1. The unit dose container complies with the Class A or Class B standard described in USP XX, General Tests, Single-Unit Containers and Unit-Dose Containers for Capsules and Tablets (page 955);
2. The expiration date does not exceed six months; and
3. The six-month expiration period does not exceed 25 percent of the remaining time between the date of repackaging and expiration date on the original manufacturer's bulk container of the drug repackaged, and the bulk container has not been previously opened. This policy only applies to solid and liquid oral dosage forms in unit dose containers. FDA will continue to impose all requirements on other dosage forms and other types of packages.

Exceptions: This policy does not apply to antibiotics or to drugs with well-known stability problems, such as nitroglycerin, oral digoxin, or chlorambucil tablets. (Abstracted from FDA CPG 71326.17)

Recommended: See: *supra* as to indemnity and guarantee.

Following study of this chapter, it might be helpful for staff review, to discuss specific guides provided by the FDA to their field staff and others, that are pertinent as Regulatory Action Guidance.

Sec. 430.200 Repackaging of Drug Products—Testing/ Examination Under CGMPs (CPG 7132.13)

BACKGROUND:

Questions have periodically arisen regarding how various testing and/or examination requirements under the CGMP regulations (21 CFR Parts 210 and 211) are to be applied to

repackers of finished dosage form drugs. In particular, there have been questions regarding whether it is appropriate to apply various “component” requirements in the CGMPRs (such as those under Section 211.84 concerning identity testing and analysis or receipt of a report of analysis for purity, strength, and quality) to finished dosage form drugs which an establishment receives and repackages. It has also been questioned how the requirements under 211.165 are to be applied to repackers, insofar as the requirements for appropriate laboratory determination for identity and strength of each active ingredient prior to release are concerned.

We have carefully considered the suitability of applying the requirements concerning “components” in the CGMPRs to repackers of finished dosage form drugs. Due to the definitions of “component” under 210.3(b)(3) and “drug product” under 210.3(b)(4), we have concluded that the requirements for “components” under Part 211 cannot be suitably applied to finished dosage form drugs which are received by an establishment and repackaged without alteration to the “drug product” itself.

In the preamble to the final order for the CGMP regulations, it is pointed out in regards to a manufacturer that there is no intent under 211.165(a), once the product is in its finished dosage form, to require potency testing of both the bulk and packaged drug product phases, and that manufacturers could choose to do potency assays at either phase (43 FR 45062, paragraph 389). We believe a similar principle is applicable to drug product repackers; where the manufacturer of the finished dosage form in a bulk container is required to perform appropriate analytical testing for all appropriate specifications, including the identity and strength of each active ingredient, we do not consider it necessary for the repacker to repeat such testing upon such drug products he receives and repacks with label declarations consistent with those on the bulk container and without altering the properties of the finished dosage form product.

POLICY:

Generally, we do not consider the CGMP regulations (21 CFR Parts 210 and 211) to require repackers of finished dosage form drugs to perform analytical testing such as chemical identity tests or assays, or to require receipt of reports of analysis, on a batch-by-batch basis for drug products which are repacked under the following circumstances:

1. The incoming bulk containers of finished dosage form drug products are received in intact, undamaged containers which are completely and properly labeled as received, and there is no reason to suspect they have been subjected to improper storage or transit conditions prior to receipt;
2. The repacking operations are conducted under conditions which assure that the properties of the incoming drug product are not altered;
3. The repackaged containers are labeled with the same substantive labeling declarations (e.g., identity, strength, and directions for use) concerning the properties and use of the drug product which are consistent with the labeling on the incoming bulk containers.

Under such circumstances we consider that requirements for appropriate specifications and testing/examination procedures for repacked drug products will be met by an appro-

priate system involving examination of the labeling and sufficient organoleptic examination of the drug product to confirm its identity in accordance with corresponding specifications established by the repacker.

The policy in this Compliance Policy Guide applies only to the question of adequate batch-to-batch testing/examination criteria for routine acceptance and release of drug products which are repacked. It does not alter any testing which repackers may be required to perform on drug products from other standpoints, such as any stability testing required in order to establish appropriate expiration dates in the container-closure system used by the repacker, testing which may be required to determine the suitability of the repacker's drug product containers and closures, testing which may be necessary to establish appropriate time limits for the completion of each phase of production, or testing which may be required on non-penicillin drug products for the presence of penicillin.

Issued: 7/1/81

Sec. 430.100 Unit Dose Labeling for Solid and Liquid Oral Dosage Forms (CPG 7132b.10)

BACKGROUND:

In recent years the pharmaceutical industry has responded to an increased demand for drug products which are packaged for "unit dose" dispensing, i.e., the delivery of a single dose of a drug to the patient at the time of administration for institutional use, e.g., hospitals. The drug product is dispensed in a unit dose container—a non-reusable container designed to hold a quantity of drug intended for administration (other than the parenteral route) as a single dose, directly from the container, employed generally in a hospital unit dose system. The advantages of unit dose dispensing are that the drug is fully identifiable and the integrity of the dosage form is protected until the actual moment of administration. If the drug is not used and the container is intact, the drug may be retrieved and redispensed without compromising its integrity.

In view of the intended use of unit dose packaging, each unit dose container is regarded as a drug in package form subject to all requirements of the Act and implementing regulations. However, the pertinent labeling regulations [21 CFR 201.10(i) and 201.100] present problems in interpretation in that they are inconsistent with respect to exemptions for containers too small or otherwise unable to accommodate a label with sufficient space to bear all mandatory information. As a result of several recent regulatory actions emphasizing these inconsistencies, the regulations will be rewritten in the future to clarify the requirements.

Because of the general lack of uniformity in the labeling for unit dose containers due to inconsistent interpretations of the regulations, or to a lack of knowledge of unit dose labeling requirements, we are issuing this Compliance Policy Guide (CPG).

This CPG does not encompass "Unit of Use" packaging which is defined as a method of preparing a legend medication in an original container, sealed and labeled, prelabeled by the manufacturer, and containing sufficient medication for one normal

course of therapy. (Reference: Proceedings Unit of Use Packaging Conference, January 24–26, 1979).

POLICY:

Until the regulations are revised, the attached document describes the labeling requirements for oral solid and liquid dosage forms packaged in unit dose containers. The requirements apply to all firms which package drugs into unit dose containers.

Since unit dosage forms are primarily intended for institutional use rather than sale to the general public, we will not require the warnings described in 21 CFR, Part 369 or the statements described under item 6.b. (Section I and II) of Attachment A to be on the label; however, this information must appear elsewhere in the labeling.

Where unit dose repacking is performed by a single facility for a closed membership or group (e.g., “shared services”) a current package insert, bearing adequate directions for use, located on the premises of each member to whom the repacked goods are shipped is regarded as satisfying this requirement. The absence of such a current package insert on the premises of a member to which a drug product is shipped will cause that drug product to be misbranded.

Solid and liquid oral dosage forms in unit dose containers shall be deemed misbranded under Section 502 of the Act if they deviate from the attached list of requirements.

Other unit dose forms, e.g., topical ointments/creams, ophthalmic, etc. are not included in this document. They will be considered at a future date should circumstances warrant.

ATTACHMENT A

UNIT DOSE LABELING

I. PRESCRIPTION DRUGS (Solid and Liquid Oral Dosage Forms, e.g., Capsules, Tablets, Solutions, Elixirs, Suspensions, etc.)

The label of the actual unit dose container must bear all of the following information (except item 9).

NOTE: A firm may not claim an exemption on the basis that the label is too small to accommodate all mandatory information if all available space is not utilized or the label size can readily be made larger, or if the type size on the label can readily be made smaller without affecting the legibility of the information.

1. The established name of the drug and the quantity of the active ingredient per dosage unit, if a single active ingredient product; if a combination drug, the established name and quantity of each active ingredient per dosage unit. In each case, the label must bear the established name and quantity or proportion of any ingredient named in Section 502(e) whether active or not. For solid dosage forms, a declaration of potency per tablet/capsule will suffice;

for liquid dosage forms, the total volume shall be declared as well as the quantity or proportion of active ingredient contained therein, e.g., Cimetidine HCL Liquid 5 ml, 300 mg/5 ml or 300 mg per 5 ml; or Septra/Bactrim Suspension 5 ml, contains Trimethoprim 40 mg and Sulfamethoxazole 200 mg per 5 ml; or each 5 ml. contains...

2. The expiration date (see Attachment B). (Ref. 21 CFR 201.17, 211.137).
3. The lot or control number. [Ref. 21 CFR 201.100(b), 211.130].
4. The name and place of business of the manufacturer, packer, or distributor as provided for in 21 CFR 201.1.
5. For a drug recognized in an official compendium, the subject of an approved new drug application (NDA/ANDA) or as provided by regulation:
 - A. Required statements such as "Refrigerate", "Protect From Light", "Dilute Before Using", etc., [Ref.: FD&C Act 502(f)(1), 502(g), and 505].
 - B. Any pertinent Statement bearing on the special characteristics of the dosage form, e.g., sustained release, enteric coated, chewable, suspension, etc.; [Ref. FD&C Act 502(e), 502(a), 201(n)].
6. For any drug product not subject to 5:
 - A. Any pertinent statement bearing on special characteristics of the dosage form, e.g., sustained release, enteric coated, sublingual, chewable, solution, elixir, suspension, etc.; [Ref. FD&C Act 502(e), 502(a), 201(n)].
 - B. While not required to be on the label per se, it is strongly recommended that:
 - (1). Any pertinent statement bearing on the need for special storage conditions, e.g., "Refrigerate", "Do not Refrigerate", "Protect from Light", etc., [Ref. FD&C Act 502(f)(1)] appear on the label, and
 - (2). Any information needed to alert the health professional that a procedure(s) is necessary prior to patient administration to prepare the product as a finished dosage form, e.g., "Shake Before Using" [Ref. FD&C Act 502(f)(1)].
7. If more than one dosage unit is contained within the unit dose container (solid dosage form), the number of dosage units per container and the strength per dosage unit should be specified (e.g., two capsules; each capsule contains 300 mg. Rifampin).
8. The statement "Warning: May be habit forming" where applicable, the controlled drug substances symbol required by Drug Enforcement Administration (DEA), and the name and quantity or proportion of any substance as required by Section 502(d).
9. The National Drug Code designation is recommended, although this is not mandatory.

In addition to all of the above (except item 9), the following information must appear on the outer package from which the unit dose container is dispensed:

1. The number of unit dose containers in the package, e.g., 100 unit doses. If more than one dosage unit is within each unit dose container this should also be stated (e.g., "100 packets; each packet contains two tablets," or "100 packets of two tablets each.").

2. Full disclosure information, as detailed in 21 CFR 201.100. Where unit dose repacking is performed by a single facility for a closed membership or group (e.g., “shared services”) a current package insert bearing adequate directions for use, located on the premises of each member to whom the repacked goods are shipped is sufficient to satisfy this requirement. The absence of such a current package insert on the premises of a member to which a drug is shipped will cause that drug to be misbranded.
3. The prescription legend.

II. OVER THE COUNTER DRUGS (Solid and Liquid Oral Dosage Forms, e.g. Capsules, Tablets, Elixirs, Suspension, etc.)

The label of the actual unit dose container must bear all of the following information (except item 9).

NOTE: A firm may not claim an exemption on the basis that the label is too small to accommodate all mandatory information if all available space is not utilized, the label size can be made larger, or if the type size on the label can readily be made smaller without affecting the legibility of the information.

1. The established name of the drug if it contains a single active ingredient; if a combination drug, the established name of each active ingredient. If a compendial drug, the label must express the quantity of each therapeutically active ingredient contained in each dosage unit, e.g., Aspirin Tablets, 325 mg., (USP-General Notices), and the quantity or proportion of any ingredient, whether active or not, as required by Section 502(e).
2. The expiration date (see attachment B).
3. The lot or control number.
4. The name and place of business of the manufacturer, packer, or distributor as provided for in 21 CFR 201.1.
5. For a drug recognized in an official compendium, the subject of an approved new drug application (NDA/ANDA), or as provided by regulation:
 - A. Required statements such as “Refrigerate”, “Protect from Light”, “Dilute Before Using”, etc.; [Ref. FD&C Act 502(f)(1), 502(g), and 505].
 - B. Any pertinent statement bearing on special characteristics of the dosage form, e.g., sustained release, enteric coated, chewable, suspension, etc.; [Ref. FD&C Act 502(e), 502(a), 201(n)].
6. For any drug product not subject to 5:
 - A. Any pertinent statement bearing on special characteristics of the dosage form, e.g., sustained release, enteric coated, sublingual, chewable, solution, elixir, suspension, etc.; [Ref. FD&C Act 502(e), 502(a), 201(n)].
 - B. While not required to be on the label per se, it is strongly recommended that:
 - (1). Any pertinent statement bearing on the need for special storage conditions, e.g., “Refrigerate”, “Do not Refrigerate”, “Protect from Light”, etc., [Ref. FD&C Act 502(f)(1)], appear on the label, and

- (2). Any information needed to alert the user that a procedure(s) is necessary prior to patient administration to prepare the product for use, e.g., “Shake Well”, “Dilute Before Using” [Ref: FD&C Act 502(f)(1), 21 CFR 201.5].
7. If more than one dosage unit is contained within the unit dose container, the number of dosage units per container should be specified (e.g., two tablets aspirin; each tablet contains 325 mg).
8. The statement “Warning: May be habit forming” where applicable, the controlled drug substances symbol required by DEA, and the name and quantity or proportion of any substance required by Section 502(d).
9. The National Drug Code designation is recommended, although this is not mandatory.

In addition to all of the above (except item 9), the following information must appear on the outer package from which the unit dose container is dispensed:

1. The number of unit dose containers in the package. If more than one dosage unit is within each unit dose container this should also be stated (e.g., “100 packets; each packet contains two tablets,” or “100 packets of two tablets each.”)
2. The labeling, i.e., the outer carton or a leaflet enclosed within the package must bear adequate directions for use as specified in 21 CFR 201.5 and should include:
 - A. Statement of all conditions, purposes, or uses for which the drug product is intended.
 - B. Quantity of dose, including usual quantities for each of the uses for which it is intended and usual quantities for persons of different ages and conditions.
 - C. Frequency of administration.
 - D. Duration of administration.
 - E. Time of administration (in relation to time of meals, time of onset of symptoms, or other time factors).

ATTACHMENT B

EXPIRATION DATING OF SOLID AND LIQUID ORAL DOSAGE FORMS IN UNIT DOSE CONTAINERS. (See CPG 7132b.11).

No action will be initiated against any unit dose repackaging firm, including shared services, or drug product in unit dose container meeting all other conditions of FDA’s repackaging requirements, solely on the basis of the failure of the repackaging firm to have stability studies supporting the expiration dates used provided:

1. The unit dose container complies with the Class A or Class B standard described in the Twentieth Edition of the United States Pharmacopeia, General Tests, Single-Unit Containers and Unit-Dose Containers for Capsules and Tablets (page 955); and

2. The expiration date does not exceed six months; and
3. The six month expiration period does not exceed 25 per cent of the remaining time between the date of repackaging and the expiration date shown on the original manufacturer's bulk container of the drug repackaged, and the bulk container has not been previously opened.

This policy does not apply to antibiotics or to nitroglycerin sublingual tablets which are known to have stability problems that preclude them from being repackaged.

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Bulk Pharmaceutical Chemicals

This chapter addresses the FDA requirements and then highlights differences with respect to the European and World Health Organization (WHO) requirements.

FDA REQUIREMENTS

There appears to be universal agreement that there are significant differences between the processes used for the manufacture of dosage forms and those used for the manufacture of bulk pharmaceutical chemicals. These differences include:

- Diversity of bulk pharmaceutical chemicals (BPC) manufacturing operations, which can range from a one-step synthesis to a multistep process that may take several weeks to complete.

- The BPC process being designed to improve purification, whereas this is not possible for dosage forms.

- The output, being a single chemical entity, is easier to evaluate for quality. Many BPCs have other nonpharmaceutical uses.

- Easier to achieve and confirm homogeneity with a single material.

At one time, some of the BPC industry supported the concept that quality could be assured by testing alone and that GMPs and validation were irrelevant. This attitude is no longer prevalent, and current discussions relate to identification

of the point in the production process where GMP compliance is necessary and to what extent.

The CGMP regulations (21 CFR 210 and 211) apply only to dosage forms and are to be used only as a general guide for BPCs. However, the definition of “drug” in the Food, Drug and Cosmetic Act includes both dosage forms and BPCs, and Section 510 (a)(2)(B) requires that all drugs are manufactured, processed, packed, and held in accordance with the GMPs. This creates a problem since implementation of the Act requires compliance but there are no GMPs specific to BPCs. The FDA approach was to apply the basic concepts of the CGMPs while accepting that the level and extent of compliance can be varied in relation to the stage in the manufacturing process and the end use of the BPC. This naturally leads to considerable variability in application and interpretation. In an effort to reduce this variability the FDA, in 1991, issued a revised version of the Guide to the Inspection of Bulk Pharmaceutical Chemicals. This is not a regulation but only a guide to provide focus and support for FDA field investigators. However, compliance with the Guide has become a requirement for approval in the FDA Pre-Approval Inspection procedure. A draft guidance document on BPC-GMPs to be issued by the FDA and the European Union remains unfinalized.

In the introduction to the FDA Guide, it is clearly stated that 21 CFR 210 and 211 should be applied to BPCs except that in most cases “it is neither feasible nor required to apply rigid controls during the early processing steps.” A definition of “early processing steps” is obviously critical to assure compliance. The Guide states that “it is reasonable to expect GMP concepts to start to become applicable at that point where a starting material enters a biological or chemical synthesis or series of processing steps, where it is known that the end product will be a BPC.” It is acknowledged that this does not involve going back in the synthetic chain to basic raw materials such as oil, minerals, and botanicals. However, the definition is much too loose for consistent interpretation. More detail is provided later in the Guide, but an alternative definition that is more precise (Suggested Reading number 4) is “the point onwards in the synthesis where analytically well defined, isolatable, and stable starting materials are introduced into the synthesis, and where the analytical specifications of these starting materials is alone sufficient to ensure the quality of the BPC, independent of the method used to obtain the starting material. This point is where lack of adequate control procedures and products could result in the manufacture of product not meeting the defined specifications.” In order to minimize the potential for conflict over this issue, companies should provide a scientific rationale for their defined starting point.

Another key issue is the scope of the term “bulk drug substance.” The Guide indicates that there is no absolute definition but provides three possible criteria:

There is no recognized nondrug commercial use for the chemical.

When a chemical reaches a point in its isolation and purification where it is intended that it will be used in a drug product.

When a chemical is sold to a pharmaceutical company for use in a drug product.

As defined, these criteria would include every ingredient in a dosage form, and the Guide does indicate that excipient manufacturers are not exempt from GMP compliance but that inspection will only be “for cause.” These statements would appear to have little value since most excipient manufacturers make little attempt to comply fully with GMPs. In 1995 the International Pharmaceutical Excipients Council issued its own draft GMPs. These too would appear to be of limited value since they would presumably be applied only by members of IPEC.

The details provided in the Guide are meant to supplement the dosage form CGMPs with information specific to BPCs. Some of the unique issues emphasized are outlined next.

BUILDINGS AND FACILITIES

A major emphasis is the potential for cross-contamination, especially at the finishing stages of filtration, drying, and packaging. Air-handling systems are to be designed to prevent cross-contamination, but no guidance is given on what conditions are appropriate. Many chemical operations take place in closed equipment in environments with no special air handling except possibly local dust extraction at charge areas to vessels. Data should be available to demonstrate that operational practices do not constitute a potential for cross-contamination.

Separate facilities are required for penicillin (as for dosage forms) and are also “encouraged” for certain steroids, cephalosporins, alkaloids, hazardous or toxic drugs, and pesticides. This is more extensive than for dosage forms.

There is an acknowledgment that some starting materials, especially those of plant origin, may be contaminated by insects or animal feces, but a company must attempt to prevent this contamination from spreading.

Potable water may be used in the preparation of BPCs provided it meets the regulatory requirements for drinking water.

Well water must be tested, but the FDA does allow reliance on data provided by municipal water authorities for their supplies. It would seem appropriate, from time to time, to recheck the water quality at the point where it enters the plant since this may be a long distance away from the municipal testing point.

Where purified water is used, the process must be validated with rigorous microbial controls. There is a statement that in the later processing steps, such as washing of filter cakes or aqueous crystallization, the water should be of a higher quality than purified water. This is especially recommended if the BPC

is for use in a parenteral product. This requirement is rather vague and possibly superfluous if purified water produces a BPC meeting the microbial (and endotoxin) specification.

The difficulties associated with production of sterile BPCs are acknowledged and additional detail is provided in the Sterile Drug Process Inspections Compliance Program (CP 7356.002A). The BPC industry, via a PhRMA Position Paper, has also addressed this important topic. The key areas include:

- Validation of support systems such as water, compressed air, filters, clean steam, vacuum, sterilization and depyronization systems, HVAC.

- Design and operation of facilities consistent with an aseptic manufacturing environment.

- Training, gowning, operational practices, and supervision of personnel.

- Equipment designed for ease of cleaning, sterilization, and depyronization.

- Use of automation wherever possible.

- Process evaluation using placebo and/or extensive sampling and sterility testing. Validation using microbial media fills is usually impractical.

EQUIPMENT

As might be expected, the emphasis is on cleanability and potential for cross-contamination. When equipment is not readily cleanable, it is proposed that it should have dedicated usage. Requirements for cleaning are outlined but with no specific detail—records of equipment use, a defined cleaning procedure, a sampling plan (rinse solvent sampling is included), defined acceptance criteria, and a validated analytical method. There is a specific reference to the monitoring of process temperature, and it is recommended that when temperature control is important, chart recorders should be used with the charts becoming part of the batch record. If recorders are not used, the reason should be justified.

Investigators are also advised that use of equipment located outdoors is acceptable provided that the processing occurs in a closed environment. Presumably the same direction would apply to equipment located inside a facility, but with no specific environmental controls except where such controls are required to maintain product quality. The importance of more careful environmental controls during the final processing steps is noted, especially for materials to be used in parenteral production. For these latter materials the environmental quality should be similar to that used for the manufacture of dosage forms. This could be interpreted as requiring Class 100 conditions for the final stages (drying, packaging) of a BPC to be used in an aseptically filled parenteral. While this is logical for a BPC required to be sterile, it is not essential if the parenteral dosage form is sterile filtered and the BPC bioburden is low.

RAW MATERIALS

The emphasis in this section is to denote differences from dosage-form operations. Deliveries may consist of large numbers of containers, and these may remain in quarantine after release until moved for use. A quarantine system is accepted as an alternative to a designated quarantine area. Identification labels need not be provided for each bag on a film-wrapped pallet as long as the pallet labeling is adequate. This seems restrictive since as written it applies only to bagged raw materials and film-overwrapped deliveries; the same requirements could be applied to any palletized delivery (e.g., drums) even when not overwrapped. Storage of some materials and solvents in bulk is acknowledged with the associated loss of specific batch identity. External storage is also acceptable provided labeling remains legible and that containers are cleaned prior to opening. Release of hazardous materials with reliance on the manufacturer's certificate of analysis is also acceptable.

CONTAINERS, CLOSURES, AND PACKAGING COMPONENTS

There are no unique requirements except that if containers used to deliver raw materials are to be reused for storage or shipping of BPCs, a suitable polymer liner is to be used.

PRODUCTION AND PROCESS CONTROLS

The unique role of mother liquors in BPC manufacture is noted with specific reference to second-crop isolation, reuse in the next production batch, and actual recovery of the solvent. Various acceptable uses of blending are described—to combine several smaller batches into one larger batch, to combine the multiple crystallizations/isolations from one production batch, to combine the output from the multiple use of a unit operation (e.g., centrifuge).

As with dosage forms, blending of nonconforming material with conforming material is not acceptable. However, it would seem possible that such blending could be allowed if the nonconformance related only to particle size distribution.

It is also acknowledged that some carryover from one batch to another may occur due to the physical inability to completely empty a centrifuge or processing vessel.

Validation of BPC processing is now expected. No details are provided in the Guide except that greater emphasis should be given to the later stages of production. One would anticipate that BPC manufacturers would perform some degree of “validation” for every step of a process as a means of minimizing the potential for adverse regulatory action and optimizing yields. However, the extent

of the evaluation and the degree of documentation may be less in earlier stages. Obviously manufacturers should clearly describe the rationale for defining the stages where validation applies—probably the same point at which more detailed attention to GMPs applies.

At present, FDA inspectors are advised to infer a lack of effective process validation for the BPC where there are repeated batch failures due to manufacturing process variability not attributable to equipment malfunction nor operator error.

The FDA expectation of validation support is relatively recent, and an approach similar to that initially used for dosage forms would seem to be practical. If sufficient batches have been produced, using consistent and well-documented processes, then retrospective validation may be appropriate. Usually 20–30 consecutive batches are expected. Where this situation does not apply, concurrent validation should be acceptable. For new BPCs or significant processing changes to existing BPCs, prospective validation is expected. Whichever approach is used, it must be integrated with an effective change control procedure.

Reprocessing is included in the Guide with the direction that causes and corrective action to minimize reoccurrence should be documented.

Manufacturers are expected to identify impurities and operate to defined limits. A separate Appendix on the subject is included in the Guide. Investigators are directed to compare impurity profiles from commercial batches to those in pilot batches and to batches included in the submission. Some investigators have been going beyond this directive and have been trying to apply the ICH Guidelines for Impurities to existing BPCs—identification of all impurities present at a level greater than 0.1%. At this time the ICH guidelines apply only to new BPCs. However, the USP requirements are rather general and can allow significant variability in impurities. For existing BPCs the pharmacological behavior of the material, with its inherent impurity profile, is usually well established through years of usage in the associated dosage forms. Consequently, one possible practical approach for existing BPCs would be to clearly define impurities in terms of chromatographic separation (e.g., R_f values) and relative quantification (e.g., spot size/intensity in relation to the parent compound). Although the identity of the impurity may not be known, it would be obvious if different or additional impurities were to appear in the BPC (e.g., from an alternative supplier) or if higher levels of the same impurities appeared. If this occurred, appropriate evaluation could be initiated.

IN-PROCESS TESTING

As with dosage forms, in-process testing by production personnel is acceptable provided QC has the ultimate decision making responsibility for release/rejection.

PACKAGING AND LABELING

Again there is reference to the need to protect the material during this final step of packaging. Labeling requirements are similar to those for dosage forms with respect to storage of labeling, issuance, and reconciliation.

EXPIRATION DATING OR REEVALUATION DATING

Most companies apply a reevaluation date rather than an expiration date to BPCs that are stable. This is acceptable to the FDA provided there is adequate supporting data.

LABORATORY CONTROLS

The magnitude of specifications and testing requirements for different raw materials can vary significantly, depending on the nature of the raw material and its importance in the synthetic process. BPC specifications are expected to be more comprehensive and should include limits for solvents. One might have expected that the adequacy of specifications would be the responsibility of FDA reviewing chemists rather than of investigators—whose role should be to confirm compliance.

Analytical methods are to be validated.

STABILITY TESTING

The only unique point is that storage should be in containers that “approximate the market container.” This is an acknowledgment of the impracticality of using commercial containers in some instances—50-kilo drums, silos, etc. Obviously the container/material contact surfaces should be the same and where possible offer an equivalent amount of secondary protection. For example, poly bags in a small cardboard tub may be considered equivalent to a poly liner in a 50-kilo fiberboard drum.

RESERVE SAMPLES

Reserve samples are to be retained for 1 year after distribution is complete or for 1 year after expiration or reevaluation date. These requirements apply to the manufacturer of the BPC since there are other requirements for the dosage form manufacturer.

BATCH PRODUCTION RECORDS

There is an acknowledgment that BPC manufacturers apply computer controls to many processes and that hard-copy data as found for dosage-form production may not be available. While the identification and acceptance of computer-controlled processing is laudable, it does raise the question of why the FDA found it more difficult to accept it for dosage-form production. The Guide does identify key points to be checked by an investigator when computers are used:

- (a) The system is validated (surprisingly, the term validation is not used—“systems and procedures that show the equipment is in fact performing as intended”).
- (b) Checking and calibration of equipment.
- (c) Retention of backup copies of the program.
- (d) An effective change control procedure.

EUROPEAN REQUIREMENTS

For several years the European Union (EU) accepted the Guideline for the Manufacture of Active Ingredients published by the Pharmaceutical Inspection Convention in 1987. However, it was considered that this was out of date and in February 1995 the European Commission issued draft (draft 4) “Recommendations for Good Manufacturing Practices for Active Ingredient Manufacturers.”

As the title indicates, this is a guidance document for industry but can be used as a basis for inspection, whereas the FDA Guide is for FDA investigators. The European document also clearly defines the term active ingredient: “that ingredient of a medicinal product for human or veterinary use which provides the therapeutic activity.” This is much more focused and practical than the broader but loose scope envisaged by the FDA.

As with the FDA, the point at which these GMPs apply has been defined. Again the definition is practical and clear: “that stage in production where the analytical specifications of the raw materials *alone*, together with the subsequent production steps are sufficient to ensure the quality of the active ingredient. This stage is no later than the step(s) starting with the final intermediate.” The term “final intermediate” is also defined: “the last compound produced before the reaction which, through change in covalent bond, produces the active ingredient. The final intermediate is thus starting material for the process step which produces the active ingredient.”

Since these “Recommendations” define the overall GMP requirements for the production of active ingredients, they are more comprehensive than the FDA Guide that supplements the CGMPs.

ORGANIZATION, PERSONNEL, AND TRAINING

The key role of people is emphasized in the principle that the capability and attitude of all personnel have a decisive influence upon the quality of products. Also, senior management are expected to have a formal commitment to GMP compliance; this should probably include the setting of compliance targets, the monitoring of progress, and involvement in important quality issues.

BUILDINGS AND FACILITIES

Requirements here are very general. Specific areas of note include:

- Building construction to provide adequate protection from particulate and microbial protection when handling pure and final active ingredients
- Separate production areas and equipment for highly active or sensitizing materials such as penicillins, some steroids, and cytostatic compounds.
- This is similar to the FDA Guide.

- Operation of a plant security system to prevent unauthorized access to the facility. This appears to relate to site access rather than the more usual internal restricted access.

There is no specific reference to water systems.

EQUIPMENT AND PRODUCTION

As with the FDA Guide, the concern is with the potential for cross-contamination, but less detail is provided. There is, however, emphasis on the measures to be taken to protect the product after the final filtration of the pure active ingredient. The protective measures proposed include attention to equipment design; location of equipment; avoiding use of poorly maintained equipment; avoidance of the use of inadequately purified solvents (especially recovered solvents); and use of closed drying systems. The preparation of sterile actives is expected to comply with the equipment and procedures used for sterile pharmaceuticals.

COMPUTERIZED SYSTEMS

Prospective validation is expected for new or upgraded systems, but retrospective validation is acceptable for older systems that were not validated when installed. Purchased standard software need not be validated, but configurable or specific local applications do need to be validated—a very practical approach. An effective change control procedure is required and security of access is stressed.

DOCUMENTATION

A general subsection emphasizes the importance of well-designed documentation as a basis for consistency and as an aid in the evaluation of problems.

Specifications and related test procedures are to be available. An interesting point is the statement that it is not necessary to perform every test on every batch provided there is adequate assurance, presumably from historical data and validation data, that the specification has been met. For materials a supplier Certificate of Analysis may be acceptable and for products process control data may be acceptable. Again—a sensible, practical approach.

Test records are expected to refer to the relevant specification and test method, since these can change with time. Second-person checking of records, before decision making, is also required.

Production documentation, including SOPs, should contain sufficient detail to assure consistent performance. Processing conditions may include ranges. There is an interesting dichotomy with respect to entries into production documentation. Operators making an entry are to be identified—this would allow electronic signatures. However, verification entries by supervisors require countersigning—this could be interpreted as disallowing electronic signatures. However, European regulators do appear to adopt a more pragmatic approach, and electronic entries by supervisors should also be acceptable.

Production deviations are to be reported to QC and additional action required agreed by production and QC. This is another illustration of the European approach of joint responsibility. This is further emphasized by the requirement that completed batch production records are to be signed off by the responsible person in production management.

VALIDATION

There is a requirement that production should be well controlled and that critical steps, at least from the final intermediate, should be validated. By providing definitions of prospective, retrospective, and concurrent validation, it must be assumed that all of these approaches are acceptable, presumably depending on the circumstances. For example, the author would consider the following general approach:

- (a) New products—prospective validation
- (b) Old products with consistent production processes and consistent quality performance—retrospective validation
- (c) Production changes—concurrent validation

The only additional requirements are that there should be a defined validation plan established prior to the evaluation and that includes the acceptance

criteria, and that revalidation requirements should be evaluated with respect to production changes.

CHANGE CONTROL

In addition to evaluating the potential impact of a proposed change (specification, test procedures, production processes and equipment) with respect to validation and regulatory impact, the need to notify the customer is included. While it is hoped that the changes would not affect BPC quality, customers should be given the opportunity to make their own assessment.

It is also noted that the initial batches manufactured after implementing a change should be carefully evaluated. This should be built into the change control process.

CONTRACT MANUFACTURE OR ANALYSIS

Basically this states that responsibilities should be clearly defined in writing and that the same GMP requirements apply.

MATERIALS MANAGEMENT

Materials are to be purchased using approved (and agreed?) specifications. It is also suggested that supplier evaluation may be of value. The usual requirements for storage, sampling, testing, and issue apply. However, use of raw materials before release is acceptable provided the final BPC is not released until the raw material testing is completed. This is a rare but required procedure, which is not allowed under CGMPs.

RAW MATERIALS

While supplier evaluation is optional under materials management, there is a requirement in this section to confirm that a supplier can consistently provide material meeting specifications. No guidance is given on how to provide this assurance, but experience would suggest evaluation of process definition and control, change control procedures, batch documentation, and materials performance. An effective evaluation will probably involve a site visit.

CONTAINERS, FILLING, AND LABELING

This section emphasizes the potential for cross-contamination at the filling stage, the importance of using suitable packaging materials and labeling control, and accountability.

ENGINEERING

The key role of the engineering function is emphasized in the design, installation, maintenance, and modification of buildings, equipment, and services. Engineering is also often responsible for calibration of measuring and control equipment.

QUALITY ASSURANCE AND QUALITY CONTROL

As with the dosage-form GMPs, this document clearly notes that quality assurance involves every functional unit and every individual in the company and that quality control is one functional unit with defined responsibilities.

While it is expected that all functional units are involved, it is accepted that a person or unit (quality assurance) may be assigned the responsibility of introducing, maintaining, and improving the quality assurance process.

In addition to batch records review prior to release of product, it is recommended that regular quality reviews be performed, at least annually, to confirm the consistency and adequacy of the overall quality systems. This review should include

- Trend analysis of in-process and final product test data

- Evaluation of batch failures

- Evaluation of process deviations

- Evaluation of process changes

- Evaluation of complaints

- Evaluation of recalls

The responsibilities of the quality control unit should include

- Approval of specifications and test methods

- Sampling

- Provision and maintenance of reference standards

- Analytical evaluation of problems

- Testing, approval, or rejection of raw materials, packaging materials, and products

- Stability testing

- Analytical support for complaint evaluation, process validation, and cleaning validation

- Approval of in-process control test procedures

REJECTION, RECOVERY, REPROCESSING, AND RETURNS

The introductory principle provides a unique approach. “The treatment of materials not meeting specifications should be consistent with assuring the quality of the product involved together with a responsible use of natural resources and

protection of the environment. Recovery and reprocessing of rejected materials is preferred to disposal of waste.”

While reprocessing and recovery is encouraged, all the usual checks are required to assure quality compliance of the recovered material. It is also emphasized that if reprocessing becomes routine then the basic process needs to be reevaluated.

STABILITY TESTING AND RETEST DATE

Storage conditions are not defined, but it is stated that the “design of stability studies should be based on internationally accepted concepts such as ICH.” It should be noted that at this time the ICH stability testing criteria only apply to new chemical entities and not to existing molecules. It is also indicated that retest dates may vary depending on the climatic zone of the market, and that the specification to be met at retest may differ (be tighter) than that used at time of release. Obviously the retest specification must allow for the ultimate use of the material in the dosage form and its shelf-life. Data are to be evaluated for trends—not just compliance with specification.

COMPLAINT AND RECALL PROCEDURES

There is only one significant difference from FDA requirements. Authorities are only to be informed and their advice sought in the event of a serious or life-threatening situation.

SELF-INSPECTIONS

Self-inspection is required with management responsibility for the implementation of corrective action. The audit team is to be multifunctional and not composed solely of QC/QA personnel.

RETENTION PERIODS

There is an Appendix that identifies the documents to be retained and the retention period—minimally 1 year longer than the retest period. Longer retention is expected for material distributed over a protracted period. Some documents that are not specifically related to individual batches should obviously be retained for very extended periods, e.g., development reports, validation/qualification reports.

Samples of actives are to be retained at least 1 year after the last retest date. This would seem rather premature. One would expect retention (by the dosage-form manufacturer) until at least the expiration of the dosage form in which the material was used.

WHO REQUIREMENTS

Chapter 18 of the WHO “Good Manufacturing for Pharmaceutical Products” deals with bulk drug substances—defined as pharmacologically active ingredients of pharmaceutical products. This definition is equivalent to that in the European guide and is less broad than the FDA guideline, which also includes excipients.

The WHO guide is based largely on the Pharmaceutical Inspection Convention Guidelines of 1987 and is very general in nature. The WHO allows variation from the guide to accommodate individual needs “provided the established standards of quality of the active pharmaceutical ingredients are still achieved.” The starting point for application of GMPs is to be determined by agreement between the manufacturer and the relevant regulatory authority. This point is broadly stated to be “the step from which the processes or the starting materials used have a critical influence on the quality of the active pharmaceutical ingredient.”

PERSONNEL

Requirements are general: there shall be an adequate number of personnel with the appropriate education, knowledge, skills, and training. There should be an organizational chart and defined responsibilities. Individuals with communicable diseases or lesions are to be excluded from direct contact with products.

PREMISES

The emphasis, as with other guidelines, is on the minimization of the potential for cross-contamination. Separate enclosed areas with completely separate air-handling systems are required for the production of sterile products, certain antibiotics (not defined), hormones, and cytostatic products. This is similar to FDA and European requirements. These requirements are more restrictive than those for pharmaceutical dosage forms.

As with the European guide there is no specific reference to water systems.

EQUIPMENT

Requirements are general and basic. Equipment is to be designed, constructed, located, and maintained to be suitable for use, be cleanable, minimize potential for cross-contamination, and be validated (qualified). Process monitoring equipment should be available and calibrated.

SANITATION

This requires sanitation and hygiene programs to be available. Cleaning procedures are to be validated. There is a reference here that there should be a quality standard for water—which seems out of place in this section.

DOCUMENTATION

The requirements again are basic. However, there is acceptance of electronic data processing, presumably including electronic identification, provided access to the system is restricted to authorized persons and there are appropriate security systems.

PRODUCTION

Critical steps are to be defined and validated. There is a unique but important requirement that activities in each processing area should be documented. This will be useful information in the event of a cross-contamination situation.

For the production of sterile actives it is stated that the relevant section of the product GMPs may apply to certain stages.

Surprisingly, quality control, stability studies, self-inspection and quality audits, storage, complaints, and defects and rejected materials are all included under the Production heading.

Quality control should be independent (not defined) and is responsible for specifications and test methodology; sampling procedures (but not necessarily sampling); reprocessing procedures; release or rejection of starting materials, packaging materials, and product; stability; and investigation of complaints. Review of batch documentation is not specifically included but presumably would form part of the release/reject process.

Stability studies are to be performed, but an expiration date may be replaced by a retest date.

Self-inspection by a team of experts is considered advisable.

Storage, complaints, and rejected materials subsections are basic with no surprises.

EXAMPLES OF OBSERVATIONS FROM FDA 483 CITATIONS

1. Cleaning SOPs for the bulk manufacturing facilities lacked a requirement of the maximum time that can elapse between completion of an operation and the initiation of cleaning the equipment.

2. The firm lacked a full justification or validation of the synthetic process.
3. The firm had not validated the drug substance synthetic process either retrospectively or prospectively.
4. The manufacturing facility has no formal written SOPs relating to supplier qualification.
5. The firm had not shown the fluid bed drying operation to be reproducible and predictable.
6. You did not simulate actual bulk storage conditions for stability studies.
7. Studies have almost never been performed to determine normal levels of process impurities in order to establish meaningful limits for bulk drug substance lots.
8. BPC cannot be tested by the current USP methods for organic volatile impurities.
9. The complaint list did not include at least seven complaints reviewed by the investigator.
10. The minimal cleaning procedure for hoses and pipes has not been demonstrated to be adequate in reducing the amount of product residues.
11. There is no written BPC stability program.

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Sec. 410.100 * Finished Dosage Form Drug Products In Bulk Containers—Applications Of Current Good Manufacturing Practice Regulations * (CPG 713a.06)

BACKGROUND:

* Questions have arisen concerning the application of the “umbrella” CGMP regulations, 21 CFR Parts 210 and 211 to firms which prepare dosage form drug products in bulk containers, such as tablets in fiber drums, and sterile antibiotic powders in bulk containers. Drug products in such bulk quantities are usually intended for further repacking into conventional retail packages such as bottles of 100 tablets each or vials of an antibiotic powder for reconstitution. These questions of application have, on occasion mistakenly expanded the term “bulk drug” to mean not only ingredients of drug products but also finished dosage forms in large quantities. However, in order to apply Parts 210 and 211 it is important to distinguish drug products in finished dosage forms in bulk containers from bulk drug components (i.e., ingredients intended for use in manufacturing or processing of a drug product.) *

POLICY:

The CGMP regulations set forth in 21 CFR Parts 210 and 211 apply to the preparation of finished dosage forms regardless of whether such drug products are in bulk containers or retail packaged form. This is set forth in 21 CFR 210.3(b)(4) and 211.3(a).

The CGMP regulations do not apply as binding regulations to bulk drug components. They are to be used as guidelines during the inspection of facilities manufacturing drug components (43 FR 45026, TP 42a, 9-29-78).

* Material between asterisks is new or revised *

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The Pharmacist and Total Quality Control

Some years ago, when I served as Associate Editor of *Remington's Pharmaceutical Sciences* for "Laws Governing Pharmacy," I prefaced my writing with the following statement:

The pharmacist—whether he be community practitioner in a retail establishment, a hospital pharmacist employed to prepare and dispense drugs to inpatients and outpatients, or occupied with the pharmaceutical industry in the manufacture or sale of drugs, devices, or cosmetics—must be aware of statutory law and legal relationships that affect his sphere of activity.

Essentially, this subdivides into three areas for consideration.

1. The pharmacist and his achievement and maintenance of licensure, with the requirements, responsibilities, and prerogatives that pertain. (The Pharmacy Practice Act, Regulations, and Rules of the State Board of Pharmacy.)

2. The statutory outlines of fulfilment of his particular function as a pharmacist as set out in the Federal Food, Drug and Cosmetic Act; the State Drug, Device, and Cosmetic Act and the regulations thereunder, plus any local laws that similarly pertain; and the Federal and State "Controlled Substances" laws and their regulations. This includes special laws and regulations that apply to groups of drugs deemed abusable and/or habituating on the federal, state, and local level.

3. The pharmacist practices a dynamic role in society. As a professional member of the health sciences and as an employer or employee en-

gaged in supplying products and services to the public, he must be aware of certain legal considerations that have developed out of historic common law traditions and courtroom decisions, and which overlay his daily activities.

While all that I have said above remains true and valid as we enter the new millennium, because of the dynamism of the profession today, there are many additional legal, regulatory, and even ethical guidelines of which pharmacists must be aware. Many of these have specifically arisen from the interplay of Healthcare Management Organizations, HMOs; with Pharmacy Benefit Managers (PBMs); the Internet generally, and specifically as so-called “pure-play drug-stores” who have Internet sites for direct sales; retail pharmacy chains who serve as employers, facilitators, or outlets and even pharmaceutical manufacturers as joint ventures or owners of “managed-care units.” Thus pharmacists are frequently involved as entrepreneurs in new methods of selection and distribution of finished pharmaceutical products.

Thus, as before, pharmacists often are the last safeguard for the consumer of the pharmaceuticals and are expected to use a legally anticipated degree of knowledge, competency, and experience in more than just his or her role in compounding; the pharmacist’s duties in the selection, analysis, standardization of the pharmacological moieties extend to their evaluation, their preservation, and safe distribution and use insofar as it is within the scope of their assignment.

The Durham Humphrey law in the mid-nineteenth century emphasized the primary role of the pharmacist as a dispenser. He carried out this function on the prescription of a licensed physician, dentist, or veterinarian. In other than rare instances, it was the “over the counter” (OTC) drugs that he dispensed or sold directly to the consumer.

Granted that no educational program other than pharmacy can provide the extensive knowledge of pharmaceuticals comprising complete drug expertise, changes in state laws and the pressures of federal health care programs have substantially altered aspects of the older exclusive provinces of health care practitioners. At present, therefore, there are circumstances where other than licensed physicians have qualified prescriptive authority, where nurses are no longer solely administering drugs, and where individuals not licensed as pharmacists are carrying out pharmacy functions.

To the extent that anyone other than one licensed so-to-do carries out the function of a licensed health care practitioner, the public is protected retrospectively in case of injury by recourse to our court system. Circumstances of apparent authority, supervision, selection, and training and possibilities of prior knowledge, waiver, and acceptance may be involved.

Here, we are involved only in making clear that pharmacists, or their equivalents in law in particular jurisdictions, are aware that quality control methodology attaches to their interests and should not be lightly regarded. Just as the pharmacist in earlier years of the twentieth century would not have dispensed

acetylsalicylic acid that smelled to him strongly of vinegar, today's pharmacist has to be confident in the integrity of the products he has selected for sale and distribution to persons with whom he may have no further contact.

Therefore, while pharmacists operative in the selection process may have neither the facilities, instrumentation, or training to carry out testing and validation, prudence might lead them to inquire as to product pedigree, laboratory reports, and governmental notices, as recent as available, that are pertinent to their choice and supply.

Where pharmacists are employed as inspectors, the particular agency, state or federal, will usually supply the extra training and resources necessary to assist them.

In the past decade pharmacists have been involved, privately or institutionally, in other activities for which pharmacy education has laid a foundation. Many pharmacists are involved in clinical research of pharmaceuticals as actual CRAs (clinical research assistants), as monitors, as reporters or tabulators of adverse reactions, and even in preparing test substances, comparatives and placebos. All such activities are carefully defined in the federal new drug regulations, but in the few states that regulate intrastate clinical research, the pharmacist must consider their impact also in his activities.

In very recent years, health care professionals have felt the sting of laws that impinge on their conduct as participants in information generated from medical research. Arising from *SEC* (U.S. Securities and Exchange Commission) v. *Wyatt* (civil action no. 96-5399, Central District of California, Aug. 5, 1996), additional cases have been prosecuted by the federal government to this time. In the *Wyatt* case, the government's position was that although he was not involved in the clinical testing of the anti-acne drug subject, he saved himself considerable loss in stock value by selling out when he became privy to the fact the drug was going to be dropped following Phase II of its clinical trial. A friend with whom he shared the information was likewise charged. Dr. Wyatt had come by the information by being shown the results of the clinical trial in advance by the licensor who was preparing to meet with the U.S. licensee disappointed by the clinical experience.

In these so-called inside trading cases, the Commission seeks to punish the violator by injunction and then collect civil penalties of up to three times the trader's profits or losses he avoided. Where the insider's tips to others accomplish the same result, the tipper is also deemed liable. So, all persons involved in the clinical trial and likely to gain "insider information" should be made cognizant of the dangers of disseminating confidential information to others outside of the clinical research structure, which translates into the buying or selling "of securities" (see "Clinical Trials: Insider Trading on Non Public Medical Research," Newkirk and Bresan, *FDC and Medical Device Law Digest*, Vol. 16, No. 1, March 1999).

Pharmacists have also supplied testimony as “medical experts” in cases alleging injury based on various theories of product liability. Since jurists possess considerable latitude in permitting expert testimony and such testimony requires investment of considerable time and study, plaintiffs and defense counsels are seeing pharmacists in this role frequently. I for one doubt the number will be diminished by recent federal decisions critical of the quality of expert testimony.

However, pharmacists in all forms of their practice are an excellent source of information relative to adverse reaction reporting. Nothing goes to the “misbranding” nature of labels and labeling as a civil or criminal matter more directly than this form of oversight. Most major publications available to pharmacists contain instructions and forms for adverse reaction reporting (i.e., PDR, USP/NF) and readily make extras available. Prominent pharmacy organizations such as the American Pharmaceutical Association, A.Ph.A., and the American Society of Hospital Pharmacists likewise make such provision and provide subscription to their journals, which are highly informative as to the legal responsibilities of pharmacists who undertake assignments beyond community pharmacy.

Of course, many pharmacists are directly employed in the total plan of pharmaceutical quality control by their employment in federal, state, and local health care agencies.

Having had the satisfying assignment for a number of years through federal, state, and private association of providing schools and study materials, I can tell you I know few more dedicated to their public and professional goals. When one considers that for the most part monitorial and inspection authority over licensed health care professionals is, per federal constitution, relegated to the state licensing boards in the United States, one can appreciate that these boards are themselves quality control mechanisms as to their licentiates. Indeed, I know at least one medical board (California), which following my workshop on their quality control function as to physicians, added the concept to their official title.

Long association with the National Association of Boards of Pharmacy was used to provide input to the colleges of pharmacy, as well as the boards, their attorneys, and their pharmacy inspection staffs.

THE FEDERAL MISBRANDING LAWS AS THEY GOVERN PACKAGING, REPACKAGING, LABELING, AND DISTRIBUTION BY PHARMACIES AND PHARMACISTS

The framers of the Federal Food, Drug and Cosmetic Act understood that the packaging of any article might directly affect contents in a negative way by permitting decompository and destabilizing dangerous end results—or by actu-

ally adding a harmful entity to the packaged food, drug, or cosmetic. As to the latter, truly such additives are more specifically controlled for foods than for drugs and cosmetics, thanks to the Food Additives Amendment of 1958 and identification of appropriate materials. (In CFR 2001 and Subpart F of 21 CFR Part 121.)

For drugs, there exists practical and controlling language in Section 501(a)(3), and for cosmetics, in Section 601(D) of the Federal Food, Drug and Cosmetic Act. In these subsections are proscribed the use of poisonous containers that may render the contents injurious to health. Section 501(g) requires adherence to the provisions of the drug recognized in any official compendium. This affects the pharmacy practitioner no less than the manufacturer. (See language of Section 301K of FDC Act.)

In effectuating Section 507 of the Act, the FDA has used its authority to issue detailed packaging requirements for numerous antibiotic monographs. When manufacturers wish to vary from packaging specifications stipulated in their approved new drug applications, or in antibiotic or compendial monographs, they are required to file anew and submit proofs of safety and efficacy.

The role of packaging as a form of protection external to the contents is a newer responsibility exacted by the Poison Prevention Packaging Act of 1970. In this, as in the Federal Food, Drug and Cosmetic Act, the responsibilities of the dispensing pharmacist are gravely affected.

To emphasize the pharmacist's nonexempt status with regard to packaging requirements set out in the Adulteration Statute (Section 501) 21 U.S.C. 351, and in the Misbranding Statute (Section 502) 21 U.S.C. 352, the Pharmacists Prescription Drug Dispensing Statute (Section 503(b)) 21 U.S.C. 353(b) specifically withholds exemption from the packaging requirements of paragraphs (g), (h), and (p) of Section 502:

“If he has adulterated and/or misbranded the article as per foregoing—and then dispensed it, he is a candidate for suspension or revocation of his license through board or agency action. He is also a candidate for defendancy in a lawsuit on grounds of negligence or breach of warranty. Of course, under federal or state law he is subject to criminal prosecution as well.” Willig, “The Influence of the FDC Act . . .”, FDC LJ Oct 1973, page 653.

Neither community nor hospital pharmacists are apt to be tableting or encapsulating in bulk. However, if these functions are performed other than on an extempore basis in a quantity essential for filling a patient's needs, tablet or capsule content uniformity must be assured and the official compendia provide the direction and the methodology to accomplish this. With regard to specific compendial monographs, obviously the pharmacist may have the further obligation to conduct other tests such as that for tablet dissolution rates.

PHARMACIST AND THE FEDERAL ADULTERATION STATUTE (INCLUDING CURRENT GOOD MANUFACTURING PRACTICES)

For a drug to be considered an adulterated drug violative of the Federal Food, Drug and Cosmetic Act, it is not necessary that it actually be found to contain filthy or decomposed material. Nor that the drug be found unfit for use or injurious to health. It is enough if it has been manufactured, compounded, packed, repackaged, or even held under insanitary conditions. As long as there exists a reasonable possibility that conditions are such as to result in contamination of the article, that is enough. This stringency is viewed by the courts as a necessary deterrent to the occurrence of such conditions which of themselves create a likelihood that contaminated, adulterated goods will reach the consumer.

When adulterated (or misbranded) food, drug, device, or cosmetic articles are either shipped in interstate commerce—or held for sale after shipment in interstate commerce—at a warehouse, wholesaler, community or hospital pharmacy, or any other facility, it is subject to seizure and ultimate condemnation and destruction. For the same violative circumstance, the wrongdoer, whether he be shipper or holder of such goods, may be criminally prosecuted, and if found guilty, sentenced to a prison term, or fined, or both.

While the Current Good Manufacturing Procedures elaborated by the Food and Drug Administration for its federal system of anti-adulteration according to the legislative directive in the Federal Food, Drug and Cosmetic Act are aimed at manufacturing for interstate sale and distribution, they possess important legal guidelines for current good dispensing practices to which community and hospital pharmacists should be responsive. It has also, however, been applied to seize and condemn products in local pharmacy usage, as adulterated.

The FDA papers (36), 3, 1971, for example, carried this summarial paragraph:

Pharmacy stocks of commingled foods, drugs, medical devices, and cosmetics at Jacksonville, S. Dist. Fla. while held for sale the articles . . . at a retail pharmacy had been held under insanitary conditions, the circumstances of the holding of the drugs were not in conformity with current good manufacturing practices, the labels of some articles lacked the name and address of the manufacturer, packer, and/or distributor and an accurate statement of the quantity of contents . . . and the labels of some drugs lacked the established names of the drugs and the established name and quantity of each active ingredient.

Sections 501(a)(2)(A), 501(2)(B), 501(C), 502(b)(1)(2), and 502(e)(1)(A)(i)(ii) were statutory infractions noted against the pharmacy stock. The claimant eventu-

ally signed a consent decree. While the above stock received FDA attention on complaint following a fire at the pharmacy, it stands as a vigorous reminder that as long as Section 501 deals with drugs or devices at rest in the institutional or retail pharmacy and held for sale there after their prior passage through interstate commerce, every section and subsection of 501 demands the pharmacy practitioner's attention.

The FDA's view that the start of the manufacture or compounding, in accordance with a specific formula, requires the equal meeting of specifications with regard to raw materials, packaging needs, and quality control assurance, is applicable to all the foregoing.

To the pharmacist, this means starting at least with satisfactory raw materials for his pre-dispensing manufacturing and compounding. Now, for the first time, both the USP and the FDA guidelines indicate a responsibility to be sure that microbiological as well as chemical indices are met. The same criteria by which the FDA developed figures and specific findings on a number of cases of microbiological and contamination uncovered in a district study of manufacturers who make cosmetics or drugs for topical application should and can be used by pharmacists and pharmacy officials for the dermatologists prepared in advance or contemporaneously at the pharmacy level. In every state's laws affecting pharmacy practice, the anti-adulteration section requires that it be free of such contaminants, and where they exist as they await dispensing, the products are misbranded; as well, their labeling is not true of actual content because adulterants present are not stated thereon.

The latest edition of the USP, of course, has provided a guide under the title "Microbial Attributes of Non-Sterile Pharmaceutical Products" in the General Tests Chapter.

STERILITY REQUIREMENT IN DISPENSING DRUGS

For the dispensing pharmacist, in the absence of a sterility requirement established by the USP, by the FDA's labeling demands, or by the prescriber's order, there is, at least, the presumption that the presence of microorganisms does not render the dispensed product unsafe or unfit for the patient's use. The pharmacist warrants this in law under the Uniform Commercial Code, which holds him liable for dispensing a product that is merchantable and fit for its particular use unless he has specifically disclaimed these warranties.

Aside from the legal context, certainly "secundem artem" and pharmacy ethics demand no less.

Pharmacies engaged in substantial manufacture, even for their own dispensing needs, such as in large hospitals and clinics, no doubt must consider the use of preservatives along with satisfactory large-volume diluents, whether water,

syrup, alcohol, or mixtures thereof, and adequate stability studies to support the conditions of storage and use in terms of time, place, and temperature.

Therefore, aside from the misbranding concerns that community and hospital pharmacists must share when they manufacture, repackaging, or relabel drugs, they enjoy zero immunities from anti-adulteration requirements, simply because public safety and needs could neither tolerate nor condone such failures. Since this includes not merely the thrust of federal and state laws and regulations, but legally incorporates compendial criteria to be found in the USP, NF, and the Homeopathic Pharmacopeia as applicable, the responsibility carries a collateral requirement that pharmacists be informed. Since this information is carefully conveyed to every pharmacist prior to licensure, he must merely recognize his need to review and augment this knowledge when changes and advances are recorded in those self-same compendia.

The standards described in the official compendia have a legal status equivalent to those promulgated as regulations by the federal or state drug authorities. For this reason, they are often viewed less as manuals suitable for operations and more as authoritative monographs—control standards for regulatory analysis. However, within the concept of Current Good Dispensing Practices, they become important tools for evaluating one's own operative results as well as the products of others in the greater interest of the public safety and utility.

For that reason, a pharmacist who does not possess an up-to-date library of the compendia in his pharmacy is not only liable to sanctions imposed by his peers through the State Board of Pharmacy but is actually in default with regard to the concept of Current Good Dispensing Practices.

HOSPITAL OR COMMUNITY PHARMACIES EXEMPTION FROM SECTION 505 OF THE ACT

There have been statements of policy by FDA officials along these lines, however. In fact, in a speech before a national seminar on unit packaging, Director of the Office of Compliance, Bureau of Drugs, FDA, took pains to point out that the Durham Humphrey Amendment in Section 503(b) and no other section of federal law, exempts hospital or community pharmacies from the new drug approval requirements of Section 505 of the Act. He expressly directed this comment to remind those who prepare to move into unit-dosage repackaging of drugs covered under an approved new drug application or abbreviated new drug application that they must file for and receive an approved supplementary new drug application for the product before they can legally manufacture and distribute it.

The NDA for dosage-form pharmaceuticals includes specifications for the packaging to be used, with adequate back-up data to establish that the pack-

aging material is suitable to assure integrity of the drug. If the NDA which has been approved (for the manufacturer to market a new drug or dosage form) does not provide for a new type of packaging or labeling, or new facilities for the packaging and labeling, of the New Drug for which an approval is in effect, a supplemental NDA is required.

For approval of such a supplemental NDA, the burden upon a community or hospital pharmacy is, with rare exception, simply unrealistic to contemplate.

Again, notice that there exists the fine line of difference between advance preparation and contemporaneous dispensing.

However, 301(k) prohibits adulteration and misbranding while drugs are in the pharmacist's possession rather than compounding new drugs at that level. *U.S. v. Kaybel, Inc.*, 430 F. 2d 1346 (C.A. 3 1970) raised some questions about the validity of this approach, suggesting that FDA instead had the burden of showing the unauthorized repackaging of an NDA-approved drug by one other than the NDA holder resulted in an adulterated or misbranded product. An Appeals Court reversed a conviction of a corporation and its officers for distributing a new drug in interstate commerce without the required New Drug Application, holding that if the manufacturer has an approved NDA for its package of the drug, repackaging by the distributor does not require a separate NDA by the distributor.

The pharmacist may dispense a unit dose without concern as to the federal law and actually does so when a doctor orders it for a patient, whether or not it is a prescription drug. In the hospital, this occurs all the time in filling chart orders. He can put three tablets in one capsule or empty two capsules into one powder paper, and so on. In fact, pursuant to the doctor's prescription, the pharmacist can compound a prescription of several ingredients, the combination of which would make the finished product a "new drug" if it were not dispensed to the prescribing practitioner's patient.

It is apparent, however, from the FDA's regulatory enactments, and policy statements by its officials, that any warranty of chemical or therapeutic equivalency on the basis of present standards and facilities is not feasible.

The FDA wishes to establish and maintain a basic regulatory proposition, that an approved NDA or supplemental NDA (or Abbreviated New Drug Application in certain designated instances) must be considered an individual license granted to a specific manufacturer or repackager, to cover a named product and a specific dosage form thereof. Further, that only subject to such an approval can the identity and the integrity of the drug product be assured when it reaches the patient. Such an approval requires the keenest application of current good manufacturing practices because the FDA wants to have a reasonable basis to believe that by such specification requirements as are established for the manufacture or repackaging, the raw material descriptions and tests, the container or packaging material, the personnel, facilities, and quality control procedures stipulated,

the named approved drug product will be consistently duplicated by the NDA or ANDA holder.

THE FEDERAL PHARMACIST DISPENSING STATUTE (SECTION 503B(1), (2), (3), (4), (5))

Having considered the potential misbranding effects on pharmacy practice situations exerted by Section 502 of the Federal Food, Drug and Cosmetic Act, and noted that violation of Section 510 regarding registration likewise results in misbranding, we must complete our consideration by analysis of Section 503(b) of the federal act commonly referred to as the Durham Humphrey Amendment.

A hospital or community pharmacy that engages in any drug manufacturing rather than simply compounding or dispensing for its own needs will probably fall completely outside of the present 503(b)(2) exemption, which reads in pertinent part:

Any drug dispensed by filling or refilling a written or oral prescription of a practitioner licensed by law to administer such drug shall be exempt from the requirements of section 502, except paragraphs (a), (2) and (3), (k) and (l) and the packaging requirements of (g), (h) and (p) . . .

Paragraph 503(b) (1) has limited such dispensing to one upon a written prescription for such drug by a practitioner qualified by state licensure to administer it, or upon an equivalently authentic oral prescription reduced promptly to a writing and filled by the pharmacist, or by oral or written authority to refill likewise recorded and filled.

To emphasize the limitation of the 503(b) exemption, the Act, with small exceptions similar in spirit, required pharmacies manufacturing or repackaging drugs for other than their own dispensing needs and services, to be registered under Section 510 of the Act or have any such drugs considered misbranded simply for having been produced without such registration.

WHEN THE DURHAM HUMPHREY EXEMPTION IS NOT APPLICABLE

In fact, it might be helpful to note exactly where and when the Durham Humphrey exemption is not applicable as stated in Section 503(b)(2).

The exemption does not apply if the labeling supplied by the pharmacist is false or misleading in any particular (502(a)), nor does it apply if the pharmacist

has dispensed it as an imitation of another drug or has put it up for sale under the name of another drug (502(1)(2)(3)). This does not preclude legally sustainable dispensing of qualified generic drugs. Further, the exemption is lost if the pharmacist dispenses insulin or antibiotics, which do not enjoy effective certification in the course of supplying part or all of a prescription for man (502k, 1).

And then to return to the loss of exemption in the event of mispackaging by the pharmacist, unless the drug is packaged and labeled as recognized in the effective official compendium, or if not so provided for, unless packaged and labeled as required by the FDA. That required manner covers drugs liable to deterioration, unless packaged in such form and manner with its label bearing a statement of such precautions noted as required to protect the public. The logical guideline for pharmacists here is to mimic the manufacturer's package, which has met specific regulatory controls, including those set out by the manufacturer's new drug application pursuant to the regulations effectuating Section 505 (21 CFR 130 et seq.).

Should the exactitudes of Section 503(b) concern pharmacists? Of course, and for two very important reasons.

- (1) Every pharmacist needs to qualify for and enjoy the exemptions it offers as he executes his dispensing function.
- (2) The statutory scheme, as emphasized by the courts in punishing physicians as well as pharmacists for dispensing violations (*DeFreese v. U.S.* 270 F 2d 737, in 1959), 15 established lawful methods for dispensing drugs upon prescription. "Anyone dispensing drugs outside of the statutory scheme violates the law."

Once a drug has been characterized by the Durham Humphrey Act (in 503(b)(1)), the federal pharmacist's dispensing law, as a "legend" drug, it must be treated as such by all. It must bear the legend constantly prior to dispensing per Section 503(b)(4).

When the exemption is not applicable because the product the pharmacist is distributing to his patron has not been ordered, or not been ordered by a qualified prescriber, were the pharmacist to dispense or distribute the drug, it would be misbranded and he the misbrander.

The law has been held to make it impossible for a nonprescriber to provide adequate labeling and advice for use of such product by a layman. 16 Minus the qualified prescriber, even the full disclosure labeling that has accompanied the medicine to the pharmacist is held insufficient. For that reason the pharmacist's dispensing in accordance with current dispensing practices always requires a bona fide practitioner-patient relationship, with such prescription meeting the minimal technical requirements of the federal law as described in 503(b)(1)(i)(ii)(iii) for

the content of the prescription and 503(b)(2) for the content of the prescription label.

I might add, almost parenthetically, that pharmacists who understand their obligations to provide safe and effective drug products are constantly refreshing their knowledge and understanding of the quality control mechanism on the retail or institutional level. Yet, even though current good dispensing practices might seem a full-time job, these very pharmacists are often leaders in extra-pharmaceutical innovation because their energy, spirit of inquiry, scientific vigor, and desire to better serve the public move them to the further parameters of pharmacy service.

MANUFACTURERS' OBLIGATION FOR FULL DISCLOSURE

While manufacturers have an obligation to supply "full-disclosure" labeling with prescription drugs and to make same available on request to practitioners who make a written request for it, pharmacists as "end-of-line" distributors also have the same obligation. This is apart from special circumstances (e.g., contraceptive pills) where additional labeling material to accompany the labeled prescription is passed on to the consumer.

State registration is sufficient for pharmacies, yet in the language of the federal law (Section 510) they must register federally where they have an export or import or other business involving processing and/or repackaging in drugs, devices or cosmetics, apart from that which provides for their business of dispensing or selling drugs at retail.

In short, whenever a pharmacy that is maintained in conformance with applicable local laws regulating the practice of pharmacy and medicine is

manufacturing, preparing, propagating, compounding or processing drugs for sale other than in the regular course of their business in dispensing prescriptions in response to prescriptions received, or in the course of selling drugs at retail,

However, it is not merely when he assumes the role of the manufacturer that the FDC Act applies to the pharmacist. It applies to him as he practices pharmacy in any manner, as analysis discloses.

Although federal law approaches the action of "repackaging" as though it were manufacture, traditionally many pharmacists have taken liberties with the exact requirements of the law. As the FDA has put it in their manual for pharmacists:

The law requires adequate directions for use in the labeling of a drug, and appropriate warnings where these are needed for the protection of the user. It is obvious that the purposes of the law are not served if the package which reaches the consumer does not bear such information.

The law provides that a pharmacist will not be charged with responsibility for having sold a misbranded over-the-counter drug if he sells it under the same labeling that was on the package when he received it. Thus, the safe course for the pharmacist is to put on the label of the repackaged article all the directions for use, warnings, ingredient statement, and any other information that is required by the law, just as they appeared on the original package. The label should, of course, declare the quantity accurately.

FDA inspectors have investigated injury cases which the drug responsible was an over-the-counter product that had been repackaged by the pharmacist and dispensed with incomplete labeling. Investigation has disclosed that a disappointingly high proportion of pharmacists do repack and sell over-the-counter products, including some relatively potent drugs, with wholly unsatisfactory labeling. This has been called to the attention of the major pharmacy organizations with a request for cooperation in securing voluntary compliance with the law.

Some of the more serious violations of this kind have been referred to State Boards of Pharmacy, or other state enforcement agencies. (The RX Legend, FDA Pub.)

Admittedly, many hospital pharmacies and high-volume prescription package quantities of prescription drugs as well as nonprescription drugs in advance. In the inflexible language of the federal statute, as well as state equivalents, they are not exempt from Section 502's labeling and packaging requirements. To avoid a technical charge of misbranding, they must repack in mimicry of the original package. The only exemption the pharmacy and pharmacist enjoy comes with the actual dispensing act under the Durham Humphrey law. Until that moment, the pharmacist is bound by Section 502 of the Act and the language of Section 301 (k).

However, considering the requirements of law and their purposes, and balancing these against the exigencies of practice needs, one develops some rationale accompanying repackaging of another manufacturer's finished dosage form.

I believe there is a fine line that distinguishes pharmacy manufacture and compounding for preparation of drug or device products in advance for future dispensing, from doing the same contemporaneously as the dispensing need arises. I think only in the latter is the pharmacist reassured as to enjoyment of the labeling exemptions from the force of Section 502. In the former instance, since the products are being held for sale after passage through interstate commerce, it seems that all of Section 502 would be applicable as to compliance requirements. I use terms like "believe," "think," and "seems" because the federal law is now rarely enforced on the community or hospital pharmacy level due to FDA manpower shortages, and I am not aware of many actual instances of enforcement based solely on "in-pharmacy" manufacturing, compounding, repackaging or relabeling insufficiencies.

The following original article emphasizes the foregoing,

Keep in a Cool Place: Pharmacy Practice as a Quality Control Mechanism

Randi Cane

Instruction labels on a prescription, such as “SHAKE WELL” or “REFRIGERATE,” are simply additional instructions for the patient. However, the pharmacist and/or manufacturer view these as essential statements that extend the life and utility of the product from the time it is manufactured until it is administered or used. The manufacturer’s quality control procedures would be futile if the distributor, wholesaler, and pharmacist failed to maintain the controls that are incorporated in product design and labeling. Without the expertise of a pharmacist, defective products could be an even greater concern in the health care system.

If a label reads, “Keep in a cool place,” the pharmacist knows that the product should be kept at a temperature of 46°F to 59°F, as defined by the USP. The pharmacist is trained to pass this information on to the patient when dispensing the drug product. Further, pharmacists have been educated to be particularly perceptive and exercise their senses of sight, smell, and even taste to conduct quality control.

Pharmacist’s Role in Quality Control

Today’s practitioner exercises judgments and makes determinations on manufacturing, compounding, or dispensing. We have at our disposal greater education, training, and state-of-the-art equipment to supplement ethical instincts than at any other time.

To be successful in assisting with quality control, the pharmacy practitioner must understand the mission and importance of this function. Additionally, pharmacists must be familiar with the state and federal laws and regulations that describe the parameters of pharmacist obligation and the concerns of society.

Ms. Cane served as a part-time assistant to the Drug Law Unit, Temple University School of Law, and as a Compliance Supervisor (FDA) for a multinational pharmaceutical manufacturer.

Every pharmacist recognizes his or her duty to the patient, which includes challenging the prescription presented if it appears to be in error in strength or dosage. The pharmacist is entrusted with the responsibility of presenting drugs to the patient in unadulterated and non-misbranded condition. A product can be deemed adulterated without containing filthy or decomposed materials.¹

Patient Instructions

When a tube of antibiotic cream that is labeled “Keep in a cool place” is delivered to the pharmacy, the pharmacist must be concerned with the integrity of the manufacturer and wholesaler. Did they keep it refrigerated? When dispensing the cream, the pharmacist should say more than just, “Keep this in a cool place.” In pharmaceutical terms, a cool place is 46°F to 59°F, while a cool place to the unknowing patient may be a freezer at 20°F. Therefore, the pharmacist must define “cool place” to the patient to assist in perpetuating the non-adulterated condition.

Drug Adulteration

The Federal Food, Drug and Cosmetic Act deals with drugs and devices stored by the wholesaler, the institutional pharmacy, or the retail pharmacy. Section 501 of the act on adulterated drugs and each subsection is significant and demands our attention. It applies not only to products that are manufactured, but also to products that are dispensed. Therefore, defective refrigerators, dirty counters, or substandard heating equipment all could be deemed as potentially causing the pharmacist to dispense adulterated drugs.

Some years ago the FDA compiled figures from several cases in which microbial contamination had been noticed in the manufacture of drugs for topical application and in some cosmetics.² This prompted a close inspection of *USP* and FDA guidelines to microbial and chemical indices. Certainly, the pharmacist would not dispense a tablet containing aspirin from a container whose neck was filled with powder and crystals and smelled like vinegar. Similar observation skills must be employed to discern signs of microbial contamination in vehicles, adjuvants, and basic compounding ingredients. In institutional practice settings, as in manufacturing, pharmacists must have a knowledge of the preservatives used for large volume diluents. Adequate sterility and stability studies must be initiated and maintained to support the conditions of storage and use.

Members of the pharmacy profession do not enjoy an exemption from the anti-adulteration regulations and statutes.

References: 1.21 USC 351; 2 U.S. v. An Article of Cosmetic, U.S. District Court N.D. Ohio (1974).

Following study of this chapter, it might be helpful for staff review, to discuss specific guides provided by the FDA to their field staff and others, that are pertinent as Regulatory Action Guidance.

SUB CHAPTER 405 ANTIBIOTICS

Sec. 405.100 Prescriptions Prepared from Certified Antibiotics (CPG 7122.01)

BACKGROUND:

FDA Policy was requested concerning the situation in which a pharmacist receives a prescription calling for an antibiotic preparation which is not commercially available but which could be prepared on an extemporaneous basis by the pharmacist, using an antibiotic preparation commercially available to him in a certified package.

POLICY:

There is no objection under the FD&C Act if a pharmacist uses packages of commercially available antibiotic products which he receives in certified form for mixing with other components in order to prepare the particular product called for in the physician's prescription. Our reply would be the same if it was necessary for the pharmacist to use two or more certified antibiotics in preparing the article called for in the physician's prescription.

The views expressed in the preceding paragraph are based on the situation in which the pharmacist merely responds to the physician's request that a noncertified antibiotic preparation be prepared for an individual case. If a pharmacist should develop an antibiotic formula and induce physicians to prescribe the article, the operation would then assume the nature of a manufacturing operation. The resulting product would require batch certification by FDA.

Issued: 10/1/80

Sec. 460.100 Hospital Pharmacies—Status as Drug Manufacturer (CPG 7132.06)

POLICY:

1. Compounding in Hospitals—Registration

We interpret Section 510 of the Federal Food, Drug, and Cosmetic Act as not requiring registration by the hospital pharmacy that compounds medication for inpatient dispensing, outpatient dispensing (sale or free), mailing to a patient within the State or out of the State, or for transferral to another unit of the

same hospital (within the State or in another State) for dispensing by that unit of the hospital. However, if the hospital pharmacy compounds medication which it sells to another hospital or a drugstore, such sale is not at "retail" and registration is required.

2. Application of the "current good manufacturing practices" regulations to hospital pharmacies.

Section 501(a)(2)(B) of the Act provides that a drug shall be deemed to be adulterated if "the methods used in, or the facilities or controls used for its manufacture, processing, packing, or holding do not conform to current good manufacturing practice" This section, through the operation of Section 301(k) is applicable to hospital pharmacies, as well as to manufacturers, whether or not the establishments are required to register with FDA under Section 510. However, the CGMP regulations set forth in 21 CFR 211 apply to those establishments which are both required to register under Section 510 and which prepare dosage forms. Therefore, if the hospital pharmacy is not required to register as described in paragraph one above, 21 CFR 211 does not apply. It is the policy of FDA not to routinely inspect such pharmacies for compliance with Section 501(a)(2)(B) if they operate within state or local laws governing the practice of pharmacy. However, when a hospital pharmacy is engaged in repacking or relabeling operations that are beyond the usual conduct of dispensing or selling drugs at retail, the exemptions in the Act cease to apply; the establishment is required to register and is subject to regular inspections under Section 704 of the Act.

3. Labeling of "prepackaged drugs"

We believe that drugs packaged for use as ward stock should be labeled with the information required by regulation 201.100(b).

4. Investigational drugs

We do not believe that preparation of investigational drugs by a hospital pharmacy for use by an investigator in the hospital or in another hospital, requires registration under Section 510 of the Act. However, if the new drug has been or is to be shipped in interstate commerce for clinical trials, the "sponsor" of the investigation should file a "Notice of Claimed Investigational Exemption for a New Drug" before the shipment is made or the trials started. This "Notice" would necessarily include the name and address of the pharmacy and provide information regarding manufacture of the new drug by the pharmacy.

Submission of Forms FD-1571, 1572, and 1573 is only required when the finished new drug or the "new drug substance" used in its manufacture is in interstate commerce.

When interstate commerce is involved and the various forms must be submitted, the hospital or some other responsible person may act as the "sponsor" and file the Form FD-1571. Such "sponsor" should obtain completed Form FD-1572 or 1573 as appropriate from the actual investigators.

The physician-investigator may delegate to a hospital pharmacist responsible to him, or any other person responsible to him, the maintenance of the required records concerning the use of the investigational drug.

5. New drug applications

We recognize that a physician may prescribe an unusual preparation that requires compounding by the pharmacy from drugs readily available for other uses and which is not generally regarded as safe and effective for the intended use. If the pharmacy merely acts to fill each individual prescription as received, it is our opinion that clearance under the “new drug” provisions of the Act is not required.

If the hospital prepares a bulk quantity of an unusual drug in anticipation of prescriptions from the physician who developed the formula, or from other physicians who have been induced to use the unusual medication, we believe the situation would then differ from the one described in the preceding paragraph. If such drug is shipped interstate or a major ingredient used in manufacturing the drug is received from an out-of-state supplier, we would regard the article as a “new drug” in interstate commerce and therefore subject to the investigational new drug regulations.

6. Prepacking

We do not believe that “prepackaging” by the hospital pharmacy for dispensing within the hospital, or for outpatient dispensing, or for transferral to another unit of the hospital, would require registration under Section 510 of the Act. However, repacking of a drug which is sold to another hospital, whether or not such other hospital is under the control of the same corporation, would require registration under Section 510.

7. Antibiotic Certification

Hospital pharmacies are not exempt from the antibiotic certification regulations. Antibiotic preparations compounded by the hospital pharmacy are subject to the applicable regulations, regardless of whether the item that is compounded by the hospital pharmacy is available in the usual commercial channels. However, we point out that the pharmacist may, without further certification, compound an antibiotic preparation on the basis of a prescription issued by a licensed practitioner, if the antibiotic ingredient used for compounding the prescription is taken from a certified container packaged for dispensing. The compounded prescription is exempt from certification “for a reasonable time to permit the delivery of the drug compounded on such prescription.”

Issued: 10/1/80

**Sec. 460.200 Manufacture, Distribution, and Promotion of
Adulterated, Misbranded, or Unapproved New
Drugs for Human Use by State-Licensed
Pharmacies (CPG 7132.16)**

BACKGROUND:

This compliance policy guide (CPG) reflects longstanding FDA policy that has been articulated in related CPGs, warning letters, and federal court decisions.

FDA recognizes that pharmacists traditionally have extemporaneously compounded and manipulated reasonable quantities of drugs upon receipt of a valid prescription for an individually identified patient from a licensed practitioner. This traditional activity is not the subject of this CPG. With respect to such activities, it is important to note that 21 U.S.C. 360(g)(1) exempts retail pharmacies from the registration requirements that include, among other things, a mandatory biennial FDA inspection. The exemption applies to “pharmacies” that operate in accordance with state law and dispense drugs “upon prescriptions of practitioners licensed to administer such drugs to patients under the care of such practitioners in the course of their professional practice, and which do not manufacture, prepare, propagate, compound, or process drugs or devices for sale other than in the regular course of their business of dispensing or selling drugs or devices at retail” (emphasis added). See also 21 U.S.C. Sections 374(a)(2) (exempting pharmacies that meet the foregoing criteria from certain inspection provisions) and 353(b)(2) (exempting drugs dispensed by filling a valid prescription from certain misbranding provisions).

It should be noted, however, that while retail pharmacies that meet the statutory criteria are exempted from certain requirements of the Federal Food, Drug, and Cosmetic Act (Act), they are not the subject of any general exemption from the new drug, adulteration, or misbranding provisions of the Act.

FDA believes that an increasing number of establishments with retail pharmacy licenses are engaged in manufacturing, distributing, and promoting unapproved new drugs for human use in a manner that is clearly outside the bounds of traditional pharmacy practice and that constitute violations of the Act. Some “pharmacies” that have sought to find shelter under and expand the scope of the exemptions identified above, have claimed that their manufacturing, distribution, and marketing practices are only retail dispensing; however, the practices of these entities are far more consistent with those of drug manufacturers and wholesalers than with retail pharmacies. The activities of the self-styled pharmacies are consistent with the activities of manufacturers in that they direct promotional activities at licensed practitioners and patients. The promotional activities include employing detail persons and hiring marketing consultants to promote the company’s specialization of compounding specific products or therapeutic classes of drugs. The firms also receive and use in large quantity bulk drug substances to manufacture unapproved drug products and to manufacture drug products in large quantity, in advance of receiving a valid prescription for the products. Moreover, the firms serve physicians and patients with whom they have no established individual or professional relationship.

When less significant violations of the Act related to a pharmacy have occurred, FDA has worked cooperatively with state regulatory agencies; generally, FDA will continue to defer such actions to state authorities. However, FDA regards the more extreme examples of the foregoing conduct as significant violations that constitute deliberate efforts to circumvent the new drug, adulteration or misbranding provisions of the Act.

There is a very real potential for causing harm to the public health when drug products are manufactured and distributed in commercial amounts without FDA’s prior approval and without adequate record keeping (to retrace and recall harmful products), without labeling, or without adequate manufacturing controls to assure the safety, purity, potency, quality, and identity of the drug product. In one recent instance, an outbreak of

eye infections in regional hospitals, and the loss of an eye by each of two patients, was attributed to a drug product compounded by a pharmacy.

FDA has issued warning letters to several firms that were clearly manufacturing drugs for human use under the guise of traditional pharmacy practice. For example, one establishment manufactured over 300,000 dosage units of albuterol sulfate and other inhalation therapy drugs per month for 6,000 patients, most of whom live out of state. Another firm manufactured a large quantity of a drug product at dosage levels that have not been determined by adequate and well controlled studies to be effective for the indicated use. A recent inspection of another company operating with a pharmacy license revealed that the firm had hundreds of bulk drug ingredients on hand to manufacture about 165 different products. A review of the manufacturing dates of the “compounded” drugs on hand during the inspection of this firm revealed that 37 products had been produced over a year prior to the inspection, six products had been made between six and eleven months prior to the inspection, and 111 products had no recorded manufacturing date.

The agency has initiated enforcement action when pharmacy practice extends beyond the reasonable and traditional practice of a retail pharmacy. The courts have upheld FDA’s interpretation in those cases. See *United States v. Sene X Eleemosynary Corp.*, 479 F. Supp. 970 (S.D. Fla. 1979). *aff’d*, [1982–1983 Transfer Binder] Food Drug Cosm. L. Rep. (CCH) para. 38,207 at 39,117 (11th Cir. 1983); *Cedars N. Towers Pharmacy, Inc., v. United States*, [1978–79 Transfer Binder] Food Drug Cosm. L. Rep. (CCH) para. 38,200 at 38,826 (S.D. Fla. Aug. 28, 1978). See also *United States v. Algon Chemical, Inc.*, 879 F.2d 1154 (3d Cir. 1989), *United States v. 9/1 Kg. Containers*, 854 F.2d 173 (7th Cir. 1988), *cert. denied*, 489 U.S. 1010 (1989), and *United States v. Rutherford*, 442 U.S. 544 (1979), regarding limitations on sale of unapproved and otherwise unlawful products to licensed practitioners.

POLICY:

FDA recognizes that a licensed pharmacist may compound drugs extemporaneously after receipt of a valid prescription for an individual patient (i.e., an oral or written order of a practitioner licensed by state law to administer or order the administration of the drug to an individual patient identified and treated by the practitioner in the course of his or her professional practice).

Pharmacies that do not otherwise engage in practices that extend beyond the limits set forth in this CPG may prepare drugs in very limited quantities before receiving a valid prescription, provided they can document a history of receiving valid prescriptions that have been generated solely within an established professional practitioner–patient–pharmacy relationship, and provided further that they maintain the prescription on file for all such products dispensed at the pharmacy as required by state law.

If a pharmacy compounds finished drugs from bulk active ingredient materials considered to be unapproved new drug substances, as defined in 21 CFR 310.3(g), such activity must be covered by an FDA-sanctioned investigational new drug application (IND) that is in effect in accordance with 21 U.S.C. Section 355(i) and 21 CFR 312.

In certain circumstances, it may be appropriate for a pharmacist to compound a small quantity of a drug that is only slightly different than an FDA-approved drug that is commercially available. In these circumstances, patient-by-patient consultation between physician and pharmacist must result in documentation that substantiates the medical need for the particular variation of the compound.

Pharmacies may not, without losing their status as retail entities, compound, provide, and dispense drugs to third parties for resale to individual patients.

FDA will generally continue to defer to state and local officials regulation of the day-to-day practice of retail pharmacy and related activities. FDA anticipates that cooperative efforts between the states and the agency will result in coordinated investigations, referrals, and follow-up actions by the states.

FDA may, in the exercise of its enforcement discretion, initiate federal enforcement actions against entities and responsible persons when the scope and nature of a pharmacy's activity raises the kinds of concerns normally associated with a manufacturer and that results in significant violations of the new drug, adulteration, or misbranding provisions of the Act. In determining whether to initiate such an action, the agency will consider whether the pharmacy engages in any of the following acts:

1. Soliciting business (e.g., promoting, advertising, or using sales persons) to compound specific drug products, product classes, or therapeutic classes of drug products.
2. Compounding, regularly, or in inordinate amounts, drug products that are commercially available in the marketplace and that are essentially generic copies of commercially available, FDA-approved drug products.
3. Receiving, storing, or using drug substances without first obtaining written assurance from the supplier that each lot of the drug substance has been made in an FDA approved facility.
4. Receiving, storing, or using drug components not guaranteed or otherwise determined to meet official compendia requirements.
5. Using commercial scale manufacturing or testing equipment for compounding drug products.
6. Compounding inordinate amounts of drugs in anticipation of receiving prescriptions in relation to the amounts of drugs compounded after receiving valid prescriptions.
7. Offering compounded drug products at wholesale to other state licensed persons or commercial entities for resale.
8. Distributing inordinate amounts of compounded products out of state.
9. Failing to operate in conformance with applicable state law regulating the practice of pharmacy.

The foregoing list of factors is not intended to be exhaustive and other factors may be appropriate for consideration in a particular case.

FDA guidelines and other CPGs interpret or clarify agency positions concerning nuclear pharmacy, hospital pharmacy, shared service operations, mail order pharmacy, and the manipulation of approved drug products.

REGULATORY ACTION GUIDANCE:

Pharmacies engaged in promotion and other activities analogous to manufacturing and distributing drugs for human use are subject to the same provisions of the Act as manufacturers. District offices are encouraged to consult with state regulatory authorities to assure coherent application of this CPG to establishments which are operating outside of the traditional practice of pharmacy.

FDA-initiated regulatory action may include issuing a warning letter, seizure, injunction, and/or prosecution. Charges may include, but need not be limited to, violations of 21 U.S.C. Sections 351(a)(2)(B), 352(a), 352(f)(1), 352(o), and 355(a) of the Act.

Issued: 3/16/92

Sec. 460.300 Return of Unused Prescription Drugs to Pharmacy Stock (CPG 7132.09)

POLICY:

A pharmacist should not return drugs products to his stock once they have been out of his possession. It could be a dangerous practice for pharmacists to accept and return to stock the unused portions of prescriptions that are returned by patrons, because he would no longer have any assurance of the strength, quality, purity or identity of the articles.

Many state boards of pharmacy have issued regulations specifically forbidding the practice. We endorse the actions of these State boards as being in the interest of public health.

The pharmacist or doctor dispensing a drug is legally responsible for all hazards of contamination or adulteration that may arise, should he mix returned portions of drugs to his shelf stocks. Some of our investigations in the past have shown that drugs returned by patrons and subsequently resold by the pharmacist were responsible for injuries.

Issued: 10/1/80

Sec. 460.400 Computerized Prescription Recordkeeping by Pharmacies (CPG 7132b.09)

BACKGROUND:

The National Association of Boards of Pharmacy (NABP) Task Force on Innovative Pharmacy Care has recommended the use of automated systems in pharmacies to keep readily retrievable and accurate records.

POLICY:

The Food and Drug Administration regards the use of a computerized prescription recordkeeping system as satisfying the statutory requirements for prescription drug recordkeeping as set forth under Section 503(b) of the Federal Food, Drug, and Cosmetic Act, provided the system includes the following NABP recommended controls:

1. The pharmacist has control over all prescriptions, i.e., the pharmacist must be able to ascertain quantities, refills remaining, time of previous filling and other information pertinent to adequate control.
2. The pharmacist responsible for the initial fill of a prescription and any subsequent refills can be readily determined.
3. The data are readily retrievable. The system must be capable of producing a listing of transactions to meet FDA and DEA regulations.
4. All prescription transactions occurring while the automated system is inoperable must be entered into the system as soon as possible, after the system is repaired.
5. Data in computerized prescription storage systems can be and is recreated in case of need.
6. The system must provide for the confidentiality of patient information.

Issued: 10/1/80

Sec. 460.425 Prescription Status when Telephoned to Recording Machine (CPG 7132b.08)

BACKGROUND:

Under Section 503(b) of the Act the dispensing of a prescription drug contrary to a written or oral prescription of a physician is an act which results in the drug being misbranded while held for sale. In some cases a physician may telephone the prescription to a pharmacist's recording machine and questions have arisen as to whether this procedure constitutes an acceptable "oral prescription" under the Act.

POLICY:

The 503(b) requirement is complied with if the pharmacist dispenses a prescription drug as ordered by the physician. The FDA considers a recorded prescription as meeting the requirements of an "oral prescription," as allowed by Section 503(b), if the pharmacist plays back the recording and concludes that the voice he or she hears is that of a physician known to the pharmacist, and there is no obvious reason for suspecting the authenticity of the recorded prescription.

Issued: 10/1/80

Sec. 460.450 Status of Mail-Order Filling of Prescriptions (CPG 7132b.07)

BACKGROUND:

The question has been raised as to whether or not filling of prescriptions through the mail is legal under Section 503(b) of the FD&C Act. Some organizations have offered mail-order prescription filling services to the general public and other organizations have filled such prescriptions only for their members. All of these organizations have generally made their appeal on the basis of cut-rate prices.

POLICY:

We have () considered the status of the mail-order filling of prescriptions under the Act. We have concluded that these transactions are legal under Section 503(b) as long as the prescriptions are written by licensed physicians, the precise drug called for is dispensed, and the drug is labeled in accordance with this section.

() Indicates material has been deleted

Issued: 7/26/76

Revised: 10/1/80, 5/22/87

Sec. 460.500 Prescription Drugs for Ships' Medicine Chests (CPG 7132.11)

BACKGROUND:

The question of supplying prescription—legend drugs for use on ships has arisen a number of times. It appears highly desirable for the medicine chest aboard a ship to be fully equipped for emergencies even though there may be no physician aboard. Under present methods of communication, the ship's officers can contact a physician by radio and at least get some guidance in the use of medications that may prove lifesaving.

POLICY:

Accordingly, we do not wish to place any obstacles in the way of stocking ships' medicine chests. We have never suggested or recommended any particular procedure that should be followed. The most that we have said is that we think the pharmacist or the firm supplying prescription drugs for use on ships should exercise reasonable care and assure themselves

that the prescription drugs are in fact going to a ship's medicine chest and are not being diverted to improper channels.

Issued: 10/1/80

Sec. 400.800 Collection and Charitable Distribution of Drugs (CPG 7132.08)

BACKGROUND:

A significant proportion of the prescription drugs distributed in the United States is in the form of free physicians samples. Not all of these samples are used by the physicians to whom they are given. As a result, many religious, philanthropic and charitable organizations conceived the idea of collecting and distributing these and drugs from other sources for charitable purposes, especially overseas—a worthy undertaking fraught with many pitfalls and hazards. Practically all of the protective provisions of the Federal Food, Drug, and Cosmetic Act were being nullified by some of these operations.

FDA's experience showed that many of the drug samples collected from physicians and other sources were of questionable quality because of:

1. Age.
2. Adverse storage conditions such as excessive temperature or moisture.
3. Detached labeling.
4. Products that had been recalled from the U.S. market for various reasons.
5. The presence of investigational drugs that are not approved for use in general medical practice.
6. Other factors.

From the legal point of view, the Federal Food, Drug, and Cosmetic Act requires that a drug distributed through charitable channels be in compliance with the applicable legal provisions in the same manner as a drug distributed commercially. Initially, the Food and Drug Administration took the position that samples of drugs intended for physicians should be used only under their professional supervision and that any other disposition of physicians samples was illegal. The courts ruled, however, that so long as the samples are held in their original packages, and not repacked they are not in violation per se, by being collected and held for sale or distribution for uses other than as "physicians samples."

The controlling decision was given in an opinion by the U.S. Court of Appeals for the Third Circuit in:

U.S. vs Various Articles of Drugs (Stanack Sales Co., Inc; Kaybel, Inc.;
William B. Mandell, T/a Mandell Pharmaceuticals; claimants), 3 circ., 1964
332 F.2d 286.

Following the above decision the FDA felt constrained to change its position; at the same

time recommending a procedure to eliminate or minimize the risks involved in such collection programs. Questions also arose concerning the division and repacking of large bulk contributions of pharmaceuticals.

POLICY:

To comply with the meaning and intent of the Federal Food, Drug, and Cosmetic Act, and to insure the safety and integrity of drugs, FDA recommends the following guidelines:

1. The sample drugs should be collected from the physician's office in their original unopened packages only by authorized collectors. The unopened samples should be placed in a carton, sealed, and sent to the responsible collection agency. (A responsible collection agency is one which is registered with the Food and Drug Administration; licensed by the appropriate health agency, if required, in the State in which it operates; and maintains its operations under the supervision of a registered pharmacist or licensed physician.) The drugs so collected should not be sent directly overseas.
2. The responsible collection agency should, under the supervision of a registered pharmacist or licensed physician at the agency's place of business, sort and screen all samples to eliminate all recalled, outdated and investigational drugs.
3. Sample drugs, after having been screened and sorted, should be sent in the original, unopened package by the agency to physicians and hospitals overseas.
4. Large bulk contributions of pharmaceuticals intended for overseas shipment may be subdivided, repackaged and labeled under the supervision of a registered pharmacist or licensed physician as indicated in (1 and 2) provided proper control procedures are observed and the repackaged product complies with the Food, Drug, and Cosmetic Act.
5. State laws which prohibit the operations provided for in these guidelines will take precedence—thus if a State's law prohibits the collection of physicians samples these guidelines would be inapplicable in that State.

Issued: 10/1/80

Sec. 446.100 Regulatory Action Regarding Approved New Drugs and Antibiotic Drug Products Subjected to Additional Processing or Other Manipulations (CPG 7132c.06)

FDA is issuing this policy guide to describe the circumstances in which the agency may initiate regulatory action regarding the marketing of approved new drugs and antibiotics that have been subjected to further processing or other manipulation, such as repacking, that is not covered by an approval under sections 505 or 507. (See U.S. v. Baxter Healthcare Corp., et al., CCH 38, 166 Docket Nos. 89-2087/8 (7th Cir. May, 1990)).

Section 505 of the Federal Food, Drug, and Cosmetic Act (the Act) requires FDA approval of any new drug prior to marketing. Under the terms of that section, approval must be based on, among other things, the processes, facilities and controls used in the manufacture of the product. This is because various aspects of the manufacturing process, such as sterilization, mixing, filling, and packaging, can have a significant effect on safety and efficacy of a drug product.

Under section 507 of the Act, FDA requires an approved application, similar to an NDA under section 505, for any antibiotic to be exempted from the statutory requirement of batch certification. Thus, the agency conducts the same review, including an inspection of the manufacturer's facility, for approval of an antibiotic under section 507 as for approval of a new drug under section 505.

Under these provisions, each step in the manufacture and processing of a new drug or antibiotic, from handling of raw ingredients to final packaging, must be approved by FDA, whether carried out by the original manufacturer or by some subsequent handler or repacker of the product. Pharmacists are not exempt from these statutory requirements; however, the agency regards mixing, packaging, and other manipulations of approved drug by licensed pharmacists, consistent with the approved labeling of the product, as an approved use of the product if conducted within the practice of pharmacy, i.e., filling prescriptions for identified patients. Processing and repacking (including repackaging) of approved drugs by pharmacists for resale to hospitals, other pharmacies, etc., are beyond the practice of pharmacy and are thus subject to the requirements of premarket approval.

The only repacking outside the practice of pharmacy that has been sanctioned in the absence of FDA approval is that of solid oral dosage forms of products already approved under section 505. See *U.S. v. Kaybel, Inc., et al.*, 430 F.2d 1346 (3d Cir. 1970) (repacking of approved Enovid (estrogen) tablets from large bottles into small bottles allowed without an additional approval under section 505).

The repacking of approved new drugs and antibiotics by entities outside the terms of the respective approvals has become much more common due to the increased demand for varied product package sizes, including products for "unit-dose" dispensing by doctors, pharmacists, and institutions. Agency policy concerning unit-dose labeling for oral and liquid oral dosage forms is stated in CPG 7132b.10 (See Sec. 430.100). The expiration dating and stability requirements for unit-dose repacked drugs are covered in CPG 7132b.11 (See Sec. 480.200). Custom repackers have responded to this increased demand by performing manipulations that are well beyond the intended uses approved in the labeling for pharmacists and physicians. Such manipulations result in new products whose safety and effectiveness have not been established. During the drug approval process, specifications are set for active ingredients, identity and limits for degradation products, sterility assurance, and closure integrity. Repacking by a new manufacturer may result in an unanticipated interaction between the pharmaceutical entity and the new packaging, such as absorption and degradation, which may affect the quality and purity of the product. **STERILE DRUG PRODUCTS:** The FDA has an even greater concern about the manipulation of approved sterile drug products, especially when the sterile container is opened or otherwise entered to conduct manipulations such as dissolving, diluting or aliquoting, re-filling, re-sterilizing, or repackaging in new containers. The moment a sterile container is opened and manipulated, a quality standard (sterility) is destroyed and previous studies

supporting the standard(s) are compromised and are no longer valid. These quality standards that include product stability and sterility must be restored.

Non-invasive manipulations may also raise questions of sterility, as when intact containers are repacked into a tray with other drugs, needles, gauze, etc., and the resulting package is sterilized and marketed as a unit for clinical use. Sterilization is an operation that must be documented and rigorously reviewed, and the FDA has consistently maintained that sterility is an absolute concept that must be ensured not only by sterility testing of the finished product, but also by validation of the sterilization process. Requirements for sterilization are covered in CPG 7132a.06 (See Sec. 410.100).

Recalls and CGMPs: Enforcement Alternatives in the United States

In [Chapter 1](#), we noted numerous remedies available to the FDA to enforce CGMPs and the Federal Food, Drug and Cosmetic (FFDC) Act generally.

In an earlier period, when the authors advised manufacturers regarding deficiencies in their current good manufacturing procedures and the question was raised as to “what could the FDA do about it?” the answer was relatively simple, as we stated it earlier in terms of case law such as *Dotterweich and Park*. Because a product demonstrably manufactured in such a deficient manner was per se adulterated, the Food and Drug Administration had the option of charging the proprietors with a crime under the statute, lack of intent notwithstanding, as was done in several cases, or using the special remedial statutory actions as for adulterated products. That is, it could make multiple seizures of the product in virtually as many geographic areas as were feasible for it to prosecute and infeasible for the manufacturer to defend. Since every adulterated product is also misbranded, the opportunities for fines could be complicated and increased, as we have seen, and notwithstanding what has already been suggested, the FDA could seek injunction to bring the product distribution to a halt.

In fact, new legislation in 1984 and 1987 amended the U.S. Code to greatly increase penalties for all federal offenses. The maximum fine for individuals is now \$100,000 for each offense and \$250,000 if the violation is a felony or causes death. For corporations the amounts are doubled. Until 1985, the maximum fines for violating the FFDC Act were \$1000 for conviction of a misdemeanor violation

for each count, and \$10,000 if the conviction was of a felony, for each count. Under the new legislation, fines in successful government prosecution on behalf of the FDA have totaled in the millions.

Many of the criminal offenses are prosecuted in the same philosophical vein of Dotterweich and Park, that is, holding corporate officers personally culpable for failure to properly supervise and protect the enterprise from the carelessness, the criminal activity, or the corruption of persons in their realm of supervision. Under the Prescription Drug Marketing Act, the larcenous behavior of the manufacturer's employees in stealing and trafficking in prescription drugs, that insecure conditions of manufacture and distribution make possible, faces serious criminal prosecution and tremendous fines.

Figures 1 through 5 are charts released by the FDA for the years 1991 and 1992 that offer some interesting insights into FDA use of recall as well as more stringent remedies. Its use of warning letters should be noted in the context of the later chapter on Inspection.

But "recalls," which have an interesting background in both legislative and administrative history, have become a major contributor to the FDA's remedial success. Let us examine that process of development.

In 1978, the FDA published a "final rule," under Title 21, Part 7, Enforcement Policy. It adds somewhat to the confusion between substantive and interpretive regulations. Indeed, since it deals with recalls, a remedy not provided for under the agency statute, it may be further in a hybrid area of definition than any

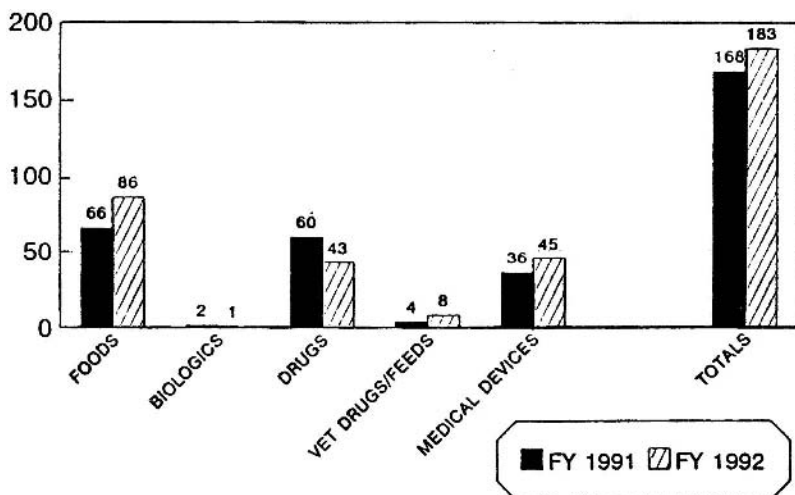


Figure 1 Seizures by the U.S. Food and Drug Administration.

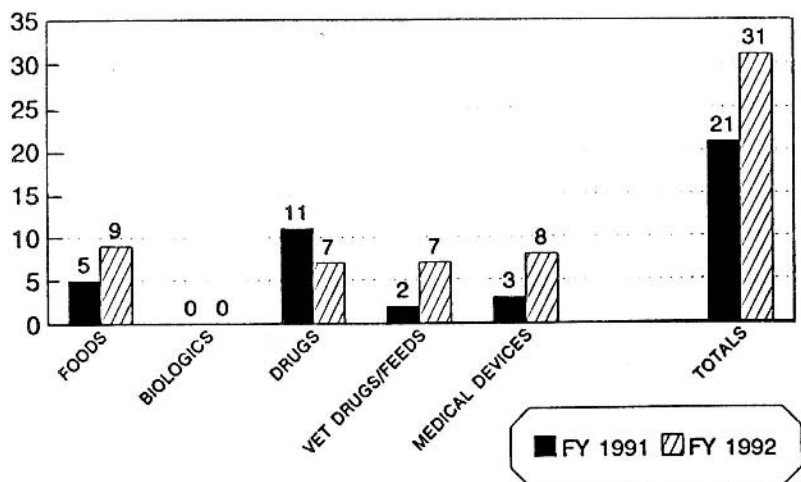


Figure 2 Injunctions by the U.S. Food and Drug Administration.

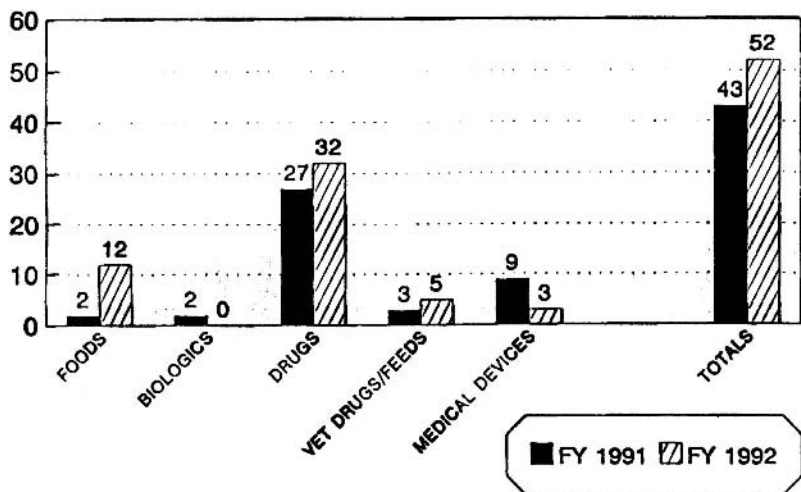


Figure 3 Prosecutions by the U.S. Food and Drug Administration.

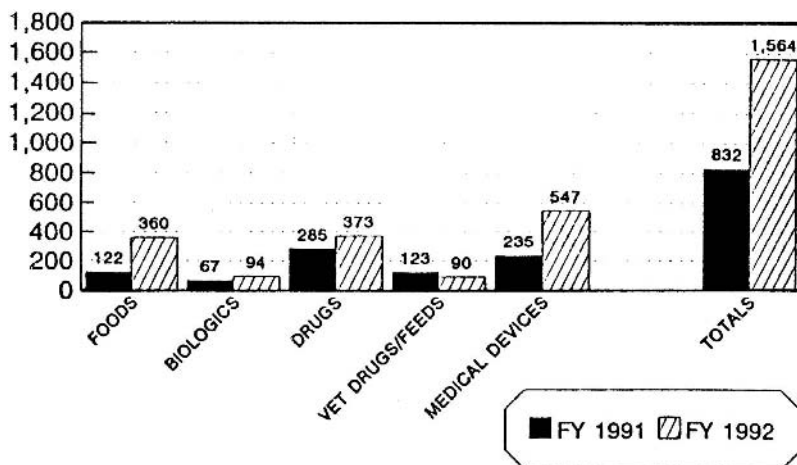


Figure 4 Warning letters by the U.S. Food and Drug Administration (includes regulatory letters through 5/23/91).

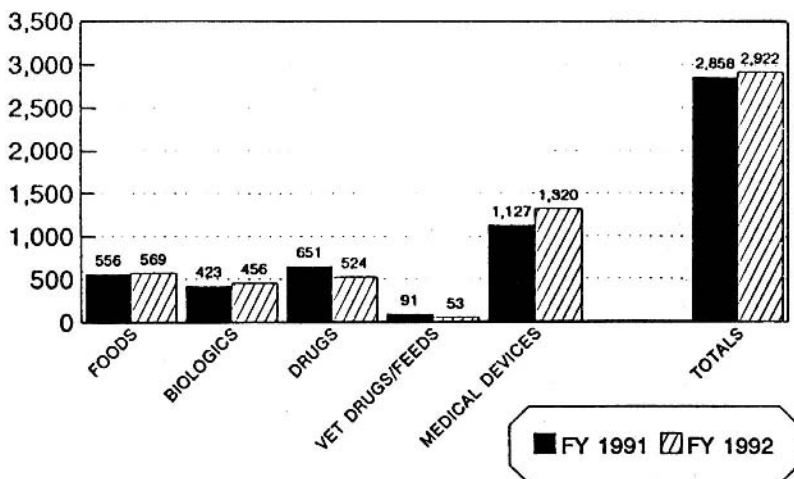


Figure 5 Recalls by the U.S. Food and Drug Administration.

other regulations. Here, by excerpts from *Federal Register*, Vol. 43, No. 117, Friday, June 16, 1978, are some basic considerations as the FDA interprets and expresses them. At the outset, you should be aware that these are not universally shared outside the agency.

Title 21—Food and Drugs

CHAPTER I—Food and Drug Administration, Department of Health, Education, and Welfare

SUBCHAPTER A—General

PART 7—ENFORCEMENT POLICY

Recalls (Including Product Corrections)—Guidelines and Policy, Procedures, and Industry Responsibilities

AGENCY: Food and Drug Administration

ACTION: Final rule.

SUMMARY: This document establishes regulations intended as guidelines that set forth the agency's policy and procedures for product recalls and that provide guidance to manufacturers and distributors of products regulated by the Food and Drug Administration (FDA) so that they may more effectively discharge their responsibilities. Recall is the most expeditious and effective method of removing or correcting defective FDA-regulated products that have been distributed commercially, particularly when those products present a danger to health. The guidelines apply to all FDA-regulated products (i.e., food, including animal feed; drugs, including in vitro diagnostic products; cosmetics; and biological products intended for human use) except electronic products subject to the Radiation Control for Health and Safety Act.

EFFECTIVE DATE: July 7, 1978.

The position of FDA can best be understood by separate discussion of the three principal areas of recall-related authority: (1) to order recalls, (2) to prescribe procedures and requirements concerning the conduct of recalls, and (3) to require the making of reports to FDA concerning recalls.

First, FDA has no authority under the Federal Food, Drug and Cosmetic Act to order a firm to recall a violative product without the aid of a court. Thus, where the agency requests a recall under these regulations, it has no authority to impose or seek sanctions for a firm's refusal to carry out the recall. (FDA may, of course, take legal action respecting the underlying violation that led to the agency's recall request; for example, it may seize an adulterated drug and/or prosecute those responsible for distributing the drug.)

Second, FDA does have authority under both the Federal Food, Drug and Cosmetic Act and the Public Health Service Act to prescribe mandatory procedures and requirements that, among other things, facilitate the conduct of recalls. The agency is not fully exercising this authority in this document in that the provisions set forth are merely guidelines rather than mandatory requirements. The agency has authority to prescribe mandatory procedures and requirements

concerning the conduct of recalls because such procedures and requirements prevent the introduction into commercial channels, or facilitate the removal from commercial channels, of adulterated, misbranded, or otherwise violative food, drugs, devices, and cosmetics.

In the preamble to the proposal, the Commissioner cited *National Confectioners Association v. Mathews*, CCH Food, Drug, & Cosm. L. Rep. ¶38.062 (D.D.C. April 14, 1976) in support of these regulations. In the *National Confectioners* case, the court upheld mandatory FDA regulations concerning good manufacturing practices for cocoa products and confectionery that included a number of recall-related requirements. The regulations, among other things, defined production lot, required coding on shipping containers or finished product packages identifying at least the plant where packed and the product lot or packaging lot, and required maintenance of distribution records. The court held that “[t]he statutory scheme as a whole and §§402(a)(4) and 701(a) in particular clearly provide an adequate statutory basis for the promulgation of the regulations.”

The district court decision in *National Confectioners* was recently upheld by the United States Court of Appeals for the District of Columbia Circuit (*National Confectioners Association v. Califano*, No. 76-1617, January 20, 1978). The court of appeals decision also strongly supports the position that the Federal Food, Drug, and Cosmetic Act provides FDA with authority to impose requirements that facilitate recalls. The court held that,

[t]he voluntary nature of recalls does not foreclose their regulation. When accommodation between the FDA and private industry has produced an efficient procedure for enforcing the Act, and when that procedure emphasizes voluntary cooperation in lieu of a more disruptive and cumbersome remedy specifically authorized by the Act, the FDA may regulate the procedure of voluntary cooperation.

Moreover, it is proper for the FDA to conclude that it cannot rely exclusively on voluntary compliance to protect the public interest. Regulations that require source codes and distribution records may be based legitimately on the need to expedite seizure when voluntary recalls are refused.

National Confectioners is one of many cases holding that FDA regulations under section 701(a) of the Federal Food, Drug and Cosmetic Act are enforceable. See, e.g., *Weinberger v. Hynson, Westcott, and Dunning, Inc.*, 412 U.S. 609 (1973).

The guidelines published in this document have purposes similar to the regulations upheld in the *National Confectioners* case, i.e., “to prevent the introduction of adulterated [articles] into commercial channels,” “to facilitate the withdrawal by the manufacturer of contaminated or suspect [articles] from the market and to enable FDA to monitor such withdrawal,” to “facilitate public warning where necessary,” and to “increase the capability of both the FDA and

the manufacturer of locating the lots which may be adulterated.” The Commissioner believes that many of the provisions in this document for the conduct of recalls (e.g., having a strategy for each recall, notifying customers of the recall, and having a current written plan for affecting recalls) could be promulgated as mandatory requirements if experience under the guidelines proves that mandatory requirements are necessary.

Several comments thought that the Commissioner was relying on the *National Confectioners* case in support of an argument that FDA could promulgate regulations under the Federal Food, Drug and Cosmetic Act, enabling the agency to order a recall. As explained above, FDA does not believe that this act provides authority to promulgate regulations enabling it to order a recall although it can, as indicated in *National Confectioners*, promulgate mandatory requirements to improve the efficiency of recalls once begun.

Third, FDA has specific authority to require the making of reports to FDA concerning recalls, such as notification that a recall is occurring, for some of the products it regulates, but not for all. The Commissioner maintains that FDA has clear authority to require such reports where there is specific statutory provision authorizing such a reporting requirement, e.g., section 505(i) and (j) (21 U.S.C. 355(i) and (j)) with respect to new drugs and sections 519 and 520(g) (21 U.S.C. 360i and 360(g)) with respect to devices; where there is specific statutory authority authorizing records inspection that includes inspection of recall-related records, e.g., section 704 (21 U.S.C. 374) with respect to prescription drugs and restricted devices; or where the product is subject to a licensing or permit requirement and reporting of recalls is a condition to the license or permit, e.g., under section 351 and 361 of the Public Health Service Act (42 U.S.C. 262 and 264) with respect to biologics. The Commissioner points out that the reporting provisions in this document are guidelines for all FDA-regulated products, despite the agency’s specific authority to promulgate mandatory reporting requirements for certain products. Other FDA regulations may contain mandatory requirements concerning recall reporting.

In its preamble to the regulations the FDA quoted *U.S. v. Park*, the modern restatement of the *U.S. v. Dotterweich* propositions of earlier FDA years. This was probably inappropriate. Thus, the FDA goes on to say:

3. A comment stated that the sanctions available to FDA are already spelled out in the Federal Food, Drug and Cosmetic Act and nowhere is there any hint that recall is one of the, or any basis to conclude that Congress intended to include recalls as a means of assuring compliance. The comment further noted that the Supreme Court’s decision in *United States v. Park*, 421 U.S. 658 (1975), makes no reference to product recall and citing this decision in the preamble to the proposed regulations cannot in any logical manner bolster the claim that recalls can be imposed upon offenders of the act. The comment asserts, therefore, that if FDA should at some future date, consider mandatory

requirements necessary, the agency should seek legislation to provide the authority which it does not now possess.

The Commissioner emphasizes that nowhere in the proposal nor in this final rule is it implied that recall is a sanction that FDA can order administratively under the Federal Food, Drug and Cosmetic Act and seek criminal prosecution of persons who do not comply with the order (excepting the repair, replacement, and refund authority for medical devices discussed in paragraph 20 below in this preamble). It is true that the preamble to the proposal cited dicta in *United States v. Park* to support the agency's position that manufacturers and distributors have the responsibility "to seek out and remedy violations when they occur***." This citation does not mean, nor was it intended to imply, that the Supreme Court's decision was being interpreted by FDA as authorizing the agency to order manufacturers or distributors to initiate recalls. However, the decision does support the view that firms engaged in the production and marketing of FDA-regulated products have by the nature of their business assumed a duty to recall their products when necessary to protect the health and well-being of the public. These recall guidelines are thus founded upon this inherent responsibility of firms and are intended to provide guidance for them to carry out this responsibility. Therefore, so long as firms continue to cooperate in discharging their product recall responsibilities, there appears to be no need for FDA to possess authority under the Federal Food, Drug and Cosmetic Act to order to recall administratively. However, if experience under these regulations proves that such authority is needed, the Commissioner agrees that the agency should seek it from Congress.

Finally, under the authority claimed, Part 7 was amended to read:

§7.1 Scope

This part governs the practices and procedures applicable to regulatory enforcement actions initiated by the Food and Drug Administration pursuant to the Federal Food, Drug and Cosmetic Act (21 U.S.C. 301 et seq.) and other laws that it administers. This part also provides guidelines for manufacturers and distributors to follow with respect to their voluntary removal or correction of marketed violative products. This part is promulgated to clarify and explain the regulatory practices and procedures of the Food and Drug Administration, enhance public understanding, improve consumer protection, and assure uniform and consistent application of practices and procedures throughout the agency.

§7.3 Definitions

- (a) "Agency" means the Food and Drug administration.
- (b) "Citation" or "cite" means a document and any attachments thereto that provide notice to a person against whom criminal prosecution is contemplated of the opportunity to present views to the agency regarding an alleged violation.
- (c) "Respondent" means a person named in a notice who presents views concerning an alleged violation either in person, by designated representative, or in writing.

(d) “Responsible individual” includes those in positions of power or authority to detect, prevent, or correct violations of the Federal Food, Drug, and Cosmetic Act.

(e) [Reserved]

(f) “Product” means an article, subject to the jurisdiction of the Food and Drug Administration, including any food, drug, and device intended for human or animal use, any cosmetic and biologic intended for human use, and any item subject to a quarantine regulation under Part 1240 of this chapter. “Product” does not include an electronic product that emits radiation and is subject to Parts 1003 and 1004 of this chapter.

(g) “Recall” means a firm’s removal or correction of a marketed product that the Food and Drug Administration considers to be in violation of the laws it administers and against which the agency would initiate legal action, e.g., seizure. “Recall” does not include a market withdrawal or a stock recovery.

(h) “Correction” means repair, modification, adjustment, relabeling, destruction, or inspection (including patient monitoring) of a product without its physical removal to some other location.

(i) “Recalling firm” means the firm that initiates a recall or, in the case of a Food and Drug Administration-requested recall, the firm that has primary responsibility for the manufacture and marketing of the product to be recalled.

(j) “Market withdrawal” means a firm’s removal or correction of a distributed product which involves a minor violation that would not be subject to legal action by the Food and Drug Administration of which involves no violation, e.g., normal stock rotation practices, routine equipment adjustments and repairs, etc.

(k) “Stock recovery” means a firm’s removal or correction of a product that has not been marketed or that has not left the direct control of the firm, i.e., the product is located on premises owned by, or under the control of, the firm and no portion of the lot has been released for sale or use.

(l) “Recall strategy” means a planned specific course of action to be taken in conducting a specific recall, which addresses the depth of recall, need for public warnings, and extent of effectiveness checks for the recall.

(m) “Recall classification” means the numerical designation, i.e., I, II, or III, assigned by the Food and Drug Administration to a particular product recall to indicate the relative degree of health hazard presented by the product being recalled.

(1) Class I is a situation in which there is a reasonable probability that the use of, or exposure to, a violative product will cause serious adverse health consequences or death.

(2) Class II is a situation in which use of, or exposure to, a violative product may cause temporary or medically reversible adverse health consequences or where the probability of serious adverse health consequences is remote.

(3) Class III is a situation in which use of, or exposure to, a violative product is not likely to cause adverse health consequences.

(n) “Consignee” means anyone who received, purchased, or used the product being recalled.

§7.40 Recall policy

(a) Recall is an effective method of removing or correcting consumer products that are in violation of laws administered by the Food and Drug Administration. Recall is a voluntary action that takes place because manufacturers and distributors carry out their responsibility to protect the public health and wellbeing from products that present a risk of injury or gross deception or are otherwise defective. This section and §§7.41 through 7.59 recognize the voluntary nature of recall by providing guidelines so that responsible firms may effectively discharge their recall responsibilities. These sections also recognize that recall is an alternative to a Food and Drug Administration-initiated court action for removing or correcting violative, distributed products by setting forth specific recall procedures for the Food and Drug Administration to monitor recalls and assess the adequacy of a firm's efforts in recall.

(b) Recall may be undertaken voluntarily and at any time by manufacturers and distributors, or at the request of the Food and Drug Administration. A request by the Food and Drug Administration that a firm recall a product is reserved for urgent situations and is to be directed to the firm that has primary responsibility for the manufacture and marketing of the product that is to be recalled.

(c) Recall is generally more appropriate and affords better protection for consumers than seizure, when many lots of product have been widely distributed. Seizure, multiple seizure, or other court action is indicated when a firm refuses to undertake a recall requested by the Food and Drug Administration, or where the agency has reason to believe that a recall would not be effective, determines that a recall is ineffective, or discovers that a violation is continuing.

§7.41 Health hazard evaluation and recall classification

(a) An evaluation of the health hazard presented by a product being recalled or considered for recall will be conducted by an ad hoc committee of Food and Drug Administration scientists and will take into account, but need not be limited to, the following factors:

(1) Whether any disease or injuries have already occurred from the use of the product.

(2) Whether any existing conditions could contribute to a clinical situation that could expose humans or animals to a health hazard. Any conclusion shall be supported as completely as possible by scientific documentation and/or statements that the conclusion is the opinion of the individual(s) making the health hazard determination.

(3) Assessment of hazard to various segments of the population, e.g., children, surgical patients, pets, livestock, etc., who are expected to be exposed to the product being considered, with particular attention paid to the hazard to those individuals who may be at greatest risk.

(4) Assessment of the degree of seriousness of the health hazard to which the populations at risk would be exposed.

(5) Assessment of the likelihood of occurrence of the hazard.

(6) Assessment of the consequences (immediate or long-range) of occurrence of the hazard.

(b) On the basis of this determination, the Food and Drug Administration will assign the recall a classification, i.e., Class I, Class II, or Class III, to indicate the relative degree of health hazard of the product being recalled or considered for recall.

§7.42 Recall strategy

(a) *General.* (1) A recall strategy that takes into account the following factors will be developed by the agency for a Food and Drug Administration-requested recall by the recalling firm for a firm-initiated recall to suit the individual circumstances of the particular recall:

(i) Results of health hazard evaluation.

(ii) Ease in identifying the product.

(iii) Degree to which the product's deficiency is obvious to the consumer or user.

(iv) Degree to which the product remains unused in the marketplace.

(v) Continued availability of essential products.

(2) The Food and Drug Administration will review the adequacy of a proposed recall strategy developed by a recalling firm and recommend changes as appropriate. A recalling firm should conduct the recall in accordance with an approved recall strategy but need not delay initiation of a recall pending review of its recall strategy.

(b) *Elements of a recall strategy.* A recall strategy will address the following elements regarding the conduct of the recall:

(1) *Depth of recall.* Depending on the product's degree of hazard and extent of distribution, the recall strategy will specify the level in the distribution chain to which the recall is to extend, as follows:

(i) Consumer or user level, which may vary with product, including any intermediate wholesale or retail level; or

(ii) Retail level, including any intermediate wholesale level; or

(iii) Wholesale level.

(2) *Public warning.* The purpose of a public warning is to alert the public that a product being recalled presents a serious hazard to health. It is reserved for urgent situations where other means for preventing the use of the recalled product appear inadequate. The Food and Drug Administration in consultation with the recalling firm will ordinarily issue such publicity. The recalling firm that decides to issue its own public warning is requested to submit its proposed public warning and plan for distribution of the warning for review and comment by the Food and Drug Administration. The recall strategy will specify whether a public warning is needed and whether it will issue as:

(i) General public warning through the general news media, either national or local as appropriate, or

(ii) Public warning through specialized news media, e.g., professional or trade press, or to specific segments of the population such as physicians, hospitals, etc.

(3) *Effectiveness checks.* The purpose of effectiveness checks is to verify that all consignees at the recall depth specified by the strategy have received notification about the recall and have taken appropriate action. The method for contacting consignees may be accomplished by personal visits, telephone calls, letters, or a combination thereof. A guide entitled “Methods for Conducting Recall Effectiveness Checks” that describes the use of these different methods is available upon request from the Hearing Clerk (HFC-20), Food and Drug Administration, Room 4-65, 5600 Fishers Lane, Rockville, MD 20857. The recalling firm will ordinarily be responsible for conducting effectiveness checks, but the Food and Drug Administration will assist in this task where necessary and appropriate. The recall strategy will specify the method(s) to be used for and the level of effectiveness checks that will be conducted, as follows:

(i) Level A—100 percent of the total number of consignees to be contacted:

(ii) Level B—Some percentage of the total number of consignees to be contacted, which percentage is to be determined on a case-by-case basis, but is greater than 10 percent and less than 100 percent of the total number of consignees;

(iii) Level C—10 percent of the total number of consignees to be contacted;

(iv) Level D—2 percent of the total number of consignees to be contacted or

(v) Level E—No effectiveness checks.

§7.45 Food and Drug Administration requested recall

(a) The Commissioner of Food and Drugs or his designee under §5.20 of this chapter may request a firm to initiate a recall when the following determinations have been made:

(1) That a product that has been distributed presents a risk of illness or injury or gross consumer deception.

(2) That the firm has not initiated a recall of the product.

(3) That an agency action is necessary to protect the public health and welfare.

(b) The Commissioner or his designee will notify the firm of this determination and of the need to begin immediately a recall of the product. Such notification will be by letter or telegram to a responsible official of the firm, but may be preceded by oral communication or by a visit from an authorized representative of the local Food and Drug Administration district office, with formal, written confirmation from the Commissioner or his designee afterward. The notification will specify the violation, the health hazard classifica-

tion of the violative product, the recall strategy, and other appropriate instructions for conducting the recall.

(c) Upon receipt of a request to recall, the firm may be asked to provide the Food and Drug Administration any or all of the information listed in Section 7.46(a). The firm, upon agreeing to the recall request, may also provide other information relevant to the agency's determination of the need for the recall or how the recall should be conducted.

Additional sections address firm-initiated recalls that are voluntary or occasioned by information from the FDA that the product(s) are violative without further instruction from the agency, 21 CFR 7.46. Other sections deal with recall communications, 21 CFR 7.49; public notification to the degree advisable in addition to the weekly FDA enforcement report, 21 CFR 7.50; and terms and descriptions required in recall status reports, 21 CFR 7.53.

A recall will be terminated when the FDA is confident product has been removed from market in accordance with the recall strategy applicable. The subject product(s) should have been removed, and proper disposition or correction made commensurate with the degree of hazard of the recalled product. FDA's written notice to the regulatee is the real termination (21 CFR 7.55).

Finally, the advice given at 21 CFR 7.59 is the advice you are following at present as a prudent organization. You should prepare and maintain a current contingency plan, in writing and communicated to others at the facility, on how to initiate and effect a proper recall that meets the regulatory requirements.

Recall is fundamentally a regulatory mechanism offering an alternative to older and more familiar statutory enforcement. But statutory increments offer more contemporary actions. Today, there are many other statutory concerns for the alleged errant manufacturer, including the explication and implication of the sentencing guidelines for organizations and responsible individuals. These of course simply demand self-surveillance and company programs to comply, or else heightened disaster may be experienced in terms of punishment. And we are not understating the statutorily enhanced debarments, blacklisting policies that have already put numerous corporate and individual entities "out of the business."

Very recently there has been a flurry of debarment orders under Section 306(a) of the Act, and as delegated pursuant to 21 CFR 5.20. These have been directed at individuals convicted of a felony under the federal law for illegal conduct related to the development or approval of a drug product, and inclusive of the process for same, as well as for misconduct relating to the regulation of a drug product (Section 305a(a)(z)(A,B)).

Any person with an approved or pending drug product application who knowingly uses the services of the person so debarred, in any capacity, during the stated period of debarment becomes subject to civil money penalties, as does the person debarred.

In addition, the FDA will not accept or review any abbreviated new drug applications (ANDAs) submitted by or with the assistance of the debarred person during his or her period of debarment.

One must understand that making a false statement to a U.S. government agency is by itself a felony federally under 18 USC 1001, as is the obstruction of an agency proceeding under 18 USC 1505. So where an employee made a false representation in a certificate of analysis regarding the potency of a particular lot of drug product and it was submitted to the FDA to support an ANDA submission, the employee's conduct was deemed felonious. Separately, when the FDA was conducting an audit, and management or an employee agent of management destroyed samples the FDA would need and use to check a previous representation made that those samples met their monograph requirements, the destruction obstructed the agency's execution of their task. That conduct was deemed felonious.

Because of the severity of this remedy, the severity of the offense, the publicity given is most effective and of course is noted in the *Federal Register*. See, in example, FR Vol. 59, No. 250, 12/30/94, P67709; FR Vol. 60, No. 7, 1/11/95, P.2767.

RECALL STATISTICS

The 1995 drug recall data provided by the FDA is shown in Table 1.

None of the recalls was classified as Class I—reasonable possibility of serious adverse health consequences or death. In fact, 126 (67%) were rated as Class III—unlikely to cause adverse health consequences. In such instances, does recall add any real value?

Dissolution and potency issues continue to be the major causes of recall (40%). However, as in previous years, packaging and labeling mix-ups also continue to be a significant problem (20%). Presumably the introduction of on-line scanning equipment will begin to reduce the incidence of these problems.

The number of recalls on suppositories is surprising considering the relatively low usage of this dosage form.

In the OTC area, one company was responsible for about 20% of the recalls. This illustrates the potential for problems when insufficient attention is paid to facilities, procedures, and people.

SUGGESTED READINGS

Urban, "FDA's Policy on Seizures, Injunctions, Civil Fines and Recalls," *Journal of the Association of Food and Drug Officials*, 56(2), 7, April 1992.

Recommended: See Appendix C as to contemporary FDA thinking on penalties.

Table 1 1995 Drug Recall Data

Dosage Form	Cause										
	Market										H
	Rx	OTC	A	B	C	D	E	F	G	II	III
Oral solids	67	25	23	17	21	20	3	3	4	38	54
Topicals	16	13	13	8	9	—	2	3	1	1	28
Injections	22	—	5	3	3	—	5	—	—	12	10
Oral liquids	14	7	4	4	7	—	3	2	7	1	14
Suppositories	2	5	4	—	—	—	—	2	—	7	6
BPCs	5	—	1	—	1	—	2	—	—	1	4
Ophthalmics	3	—	2	3	—	—	—	—	—	—	5
Inhalations	3	—	—	2	—	—	—	1	—	1	2
Nasal	—	3	2	—	—	—	—	1	—	2	1
Otic	1	1	1	1	—	—	—	—	—	—	2
Total	135	54	55	38	37	20	15	12	12	63	126

Note: Causes are A, potency; B, other specifications; C, packaging/labeling mix-ups; D, dissolution; E, contamination; F, noncompliance NDA/Monograph; G, other; H, recall class. BPCs, bulk pharmaceutical chemicals.

Following study of this chapter, it might be helpful for staff review, to discuss specific guides provided by the FDA to their field staff and others, that are pertinent as Regulatory Action Guidance.

Sec. 400.900 Class I Recalls of Prescription Drugs (CPG 7132.01)

BACKGROUND:

A Class I recall is an emergency situation involving removal from the market of a product in which the consequences are immediate or long-range, life threatening, and involve a direct cause-effect relationship. Class I recalls can, if necessary, require retrieval of the recalled article from consumers (users). The pattern of distribution of prescription drugs to consumers is different from that of other articles. Retrieval of drugs when in the possession of consumers must take into consideration the doctor/patient relationship.

POLICY:

When there is a Class I recall of a prescription drug, retail level consignees (retail, hospital, nursing home pharmacists) will be required to review their prescription files for the appropriate time period consistent with the period of distribution of the drug, in order to identify all customers to whom the recalled drug was dispensed. The pharmacist must notify those customers' physicians of the specific problem, and keep a record of the physician notifications. The physician will be responsible for deciding whether his patients are to be contacted.

If the pharmacist cannot distinguish in his prescription records between those customers to whom the lot(s) of recalled drug was dispensed, and those who received the same drug from a lot not under recall, or from a different manufacturer, then the pharmacist, as a precautionary measure, must notify the physicians of all customers who received the drug.

If retail level consignees (pharmacists, hospitals, dispensing physicians) cannot identify persons to whom a drug under Class I recall was dispensed, there must be a warning issued by FDA to the general public.

Issued: 10/1/80

Controlled Substances Safeguards (21 CFR 1300, et seq.)

There is concern with the registration and the control of the manufacture and distribution of controlled substances. There is the immediate requirement that one in such a business must annually obtain a registration for such purposes. The Drug Enforcement Administration (DEA) must register such an applicant if consistent with the public interest. In addition to the obligations of the United States under international treaties with respect to Schedule I and II substances, the statute gives standards for the public interest. These are six in number for manufacturing registration and five for distribution registration. Likewise, they are applicable to manufacture and distribution registration for Schedule III, IV, and V substances.

The additional standard for the manufacturer is that the registrant promote technical advances in the art of manufacturing these substances and the development of new substances. The other five, applicable both to manufacturers and to distributors, are that the registrant:

1. Maintains effective control against diversion of any controlled substance or any products or substances in turn compounded from the controlled substances over which it is granted authority to manufacture and/or distribute, into other than legitimate medical, scientific, and industrial channels, and produces an adequate and uninterrupted supply of these substances under legally acceptable sales condition

2. Complies with applicable state and local law
3. Has a satisfactory record with regard to prior conviction under federal or state laws relating to the manufacture and distribution of controlled substances
4. Has past experience in the manufacture of controlled substances and distribution of same, with existence in the establishment of effective controls against diversion
5. Such miscellaneous factors as may be relevant to and consistent with the public health and safety

The facility management recognizes that it has the primary operational function to establish and maintain effective systems in order to prevent diversion. Be confident that mutual cooperation between management and law enforcement personnel will result in fewer diversions and less accessibility for potential abusers. Guarding against drug loss involves the utilization and implementation of systems and procedures sufficient to confine drug theft to the lowest possible level.

EMPLOYEE SCREENING AS ONE OPERATIONAL SAFEGUARD

Concern with personnel security starts before an employee is hired. Preemployment screening for the purpose of identifying potential security problems is recognized by management to be of vital importance when choosing new employees for work in and around areas where narcotics and other scheduled controlled substances, or potent drugs, are handled. The screening program includes a careful evaluation (to the fullest extent possible in light of other laws that affect employment selection) of the applicant's personal and prior employment references. Supervisors are charged with the responsibility, by management, to make similar precautionary evaluations before transferring employees to new assignments in areas where they are first exposed, or more heavily exposed, to some role in the manufacturing process, storing, and/or shipping of bulk or finished controlled substances.

The facility management continues communication and review, with the assistance of the personnel department, as to the implementation of personnel programs that relate to these concerns. Absenteeism and alcoholism are only a few clues to the employee that may create insecurity. By attention to the health needs and problems of employees and by confidential assistance to the employees in need of diagnosis, treatment, rehabilitation, and other related procedures, management will attempt to diminish insecurity. However, all employees and union officials, where applicable, and all applicants for employment should be advised

that in any case where the company has reason to suspect a violation of this policy, the company may from time to time examine the employees' lockers, tool boxes, and personal packages on company property. The company should have a policy on drug abuse and it should be clearly stated for all employees.

RESTRICTED ACCESS AS AN OPERATIONAL SAFEGUARD

As a manufacturer and as a distributor, the facility has substantial areas to be protected against unauthorized access and egress. Access restrictions consist of people as well as equipment, mechanical and electronic devices, vaults, signs, and fences.

SUPERVISORY OVERSIGHT AS AN OPERATIONAL SAFEGUARD

As to people, the security director, by whatever title known, for each facility must be on the alert for pilferage at every level of drug handling: from the receipt of raw materials through all phases of manufacturing and processing including quality control, sampling, in-process, and reserves; through the packaging and labeling procedures, the fill, the counting, and reconciliation of estimated and actual yields; then, to the finished product storage, quarantine, and other, and to shipping. Each employee responsible must be alert to theft of dosage-form drugs, bulk raw material, and even chemical precursors. The facility contemplates careful observation of the shipping area, and when controlled substances are moved to the loading dock, it is under appropriate surveillance.

SECURITY GOALS IN TRANSPORTATION AS AN OPERATIONAL SAFEGUARD

In addition, each facility must be familiar with the transporter, selected on the basis of good reason. Elements of the same type that went into employee hiring and assignment must be used in selecting carriers. The manufacturer is concerned that controlled substances shipped are secure throughout the entire chain of handling in which it can have input. Where scheduled drugs are lost in transit, a signed statement of the facts, including a list of the controlled substances involved in the loss, is provided, along with notification to DEA and local authorities (21 CFR 1301.74).

RECORD KEEPING AS AN OPERATIONAL SAFEGUARD

The company must devise an adequate system, which it diligently seeks to test and improve, in order to keep complete and accurate records including perpetual inventories pursuant to the requirements of 21 CFR 1304.04, et seq. The effort to maintain strict product accountability is a very positive factor in carrying out the statutory command. A well-organized and properly effectuated records system is placed under strict management supervision with plant manager, director of security, and so forth, charged with proper execution.

PHYSICAL SECURITY AS AN OPERATIONAL SAFEGUARD

The DEA and the company are concerned with the provision of certain barriers and types of barriers commensurate with the quality and character of the raw materials and finished goods handled by the facility. Therefore, physical security contemplates a mixture in proper measure of mechanical and electrical apparatus directly related in the facility to maintain secure conditions for controlled substances at every phase of facility activity. Since experience by others and by the DEA indicates that losses of controlled substances usually occur when protective measures are either of such inferior quality, or simply lacking, these facilities should have incorporated physical safeguards sufficient to ensure a reasonable standard of protection for the company's controlled substances on the premises. Naturally, Schedule II compounds are afforded the maximum degree of protection in this scheme, by use of safes, vaults, and human surveillance. In addition, in other circumstances, secured rooms and wired enclosures are used, all to correspond with 21 CFR 1301.71 through 1301.74. Vaults and safes used in this facility should accord with 21 CFR 1301.72. All secured areas are backed up by effective electrical protection as required by occupancy, purpose, and schedules of materials.

SUGGESTED READINGS

See *Federal Register* Jan 31, 1989 Part II; Drug free workplace vol 54, No. 19 Government wide implementation of the Drug Free Workplace Act of 1988.

For General Legal Considerations: Drug Abuse in Industry and Business Symposium Enterprises No. Miami, FLA 33161. Sidney H. Willig, Author, W. Wayne Stewart M.D., Editor. L.C. Catalog Card No. 77-151994

The Inspection Procedure for Compliance in the United States: The Regulatee Is Inspected; The Rationale for Inspection (21 USC 373, 374)

Normally, all searches of private property, which includes both premises and papers, must be performed by authority of a search warrant issued in compliance with the warrant clause of the Fourth Amendment. Any search without a warrant is per se unreasonable, subject only to a few specifically established and well-delineated exceptions. For example, a specific exception to warrant and probable cause requirements of the Fourth Amendment is that a “search” or an inspection conducted pursuant to valid consent is constitutionally permissible.

The federal or state agency officer, who usually presents credentials and a notice of inspection to the pharmaceutical manufacturing facility, receives express or implied consent to carry out the inspection. At a later time, if the agency and the manufacturer become adversaries, the government has the burden of proving where it acted on consent of the regulatee, and that the consent was in fact freely and voluntarily given and not retracted. This does not diminish the legality of the FDA’s statutory authority to inspect or investigate a regulatee’s premises and records.

When the employee of the FDA displays his or her credentials, their nature may vary, and that may be indicative of the FDA’s concerns that are to be explored. Ordinarily the credentials will consist of Form FDA-200A and Form FDA-200B. They authorize inspection, collection of samples, access to copy and verify records, to make seizures under 702(e)(5) of the Act, and to supervise compliance operations for the enforcement of the Act.

Inspectors or investigators who present credentials consisting of Form FDA-200D have special authority for criminal investigators and may carry firearms. On such presentation or presentation under Form FDA-200E, the regulatee should understand that he or she need obtain advice from counsel promptly. With the recent increase in criminal-style enforcement, regulatees should know the difference in FDA employee credentials (21 CFR 5.35).

There is no doubt that the FDA staff can inspect and investigate with the aid of a warrant that they can procure in advance and for a lesser element of “probable cause” than what is required for a search warrant in police matters. The FDA can always go to the court to enforce its claimed right of inspection under 21 USC 374. It can enlist the federal district court’s aid under 21 USC 332, which grants such district courts jurisdiction to enjoin violations of 21 USC 331. Subsection (f) of 331 prohibits the refusal to permit entry or inspection as authorized by 21 USC 374. Thus, if the court granted the FDA an injunction, the proprietor of the manufacturing premises, or other FDA regulatee, would be enjoined from refusing entry to FDA inspectors.

The FDA can go to the court to enforce a warrant that grants the right to inspect, but often takes the position that it has a right to inspect without a warrant and that one who refuses to permit inspection can be punished for the refusal, regardless of whether inspection subsequent to the refusal results in proof of noncompliance with the adulteration, misbranding, new drug sections, or other nonsubstantive areas of the statute. Other federal agencies and state agencies have made the same argument. Indeed, in *Daley v. Weinberger*, in which a doctor suspected of distributing a compound prepared in violation of the New Drug Amendments persisted in refusal to allow inspection of her premises and her records, the FDA threatened, and the court found plausible, that the FDA might institute criminal proceedings against Dr. Daley under 21 USC 331(f) and 21 USC 333(a).

Given all these alternatives, it seems the situation should be clearly favorable to the FDA. However, the Supreme Court decisions have followed a pattern that seems to indicate that ultimate Court affirmance of the FDA view will depend upon many precedential factors. The most recent relevant decision was in *Marshall v. Barlow’s Inc.*, 436 U.S. 307, 98 S. Ct. 1816 (1978), where the Supreme Court declared that the Fourth Amendment stands between the regulatee and the use of compliance inspections by the agency charged with enforcing the law (here the Occupational Safety and Health Act). From the time of that decision, numerous controversies have arisen over the standards for administrative probable cause and over the procedures for issuing a warrant.

There are many cases to explore in considering the issue of refusing to allow an FDA inspection, or withdrawing consent for an inspection. The turning point of the modernization of this controversy was in 1967. In *Camarra v. The Municipal Court*, 387 U.S. 523, the Supreme Court met the question: Is an admin-

istrative inspection authority subject to the requirement of a warrant for entry and search of private premises? The Court answered: “Yes,” overruling *Frank v. Maryland*, 359 U.S. 367, the leading case up to that time, which had held that inspections, searches minus a warrant, were reasonable under state police power, if they were for purposes of health and sanitation, but not if they were for arms or criminal paraphernalia or narcotics. In the process, however, the Court diluted the warrant requirement in the administrative inspection case. As they put it: “Probable cause in the criminal law sense is not required. For purposes of an administrative search . . . probable cause justifying the issuance of a warrant may be based” not only on specific evidence of an existing violation, but also on a showing that “reasonable legislative or administrative standards for conducting an . . . inspection are satisfied with respect to a particular establishment,” 387 USC 538. Thus, “a warrant showing that a specific business has been chosen for . . . search on the basis of a general administrative plan for enforcement of the Act derived from neutral sources . . . and the desired frequency of the searches” (*Camarra v. The Municipal Court*) would protect the regulatee’s Fourth Amendment rights.

Somewhat simultaneously with the *Camarra* case, its prohibition of warrantless inspections without consent was held to apply to business premises, but with equal restraint and qualifications by the agency inspectors and those inspected. “A person’s office or place of business is quite as immune from warrantless search as is his kitchen or bedroom,” if the area of the commercial enterprise is not one where the public may freely enter. *See v. Seattle*, 387 U.S. 541 (1967), therefore held that minus consent, the agency official needed a warrant to search or inspect, but again alluded to such a warrant as requiring a lesser standard of probable cause. “We do not in any way imply that business premises may not reasonably be inspected in many more situations than private homes, nor do we question such accepted regulatory techniques as licensing programs which require inspections prior to operating a business or marketing a product.”

At this point, the FDA formulated an internal administrative warrant policy for inspections that were not consensual.

ADMINISTRATION INSPECTIONS WITHOUT WARRANTS FOLLOWING CAMARRA AND SEE CASES

Within the area of consent to inspect, consent refused, consent withdrawn, the inspector and the agency face a varying group of possibilities. In *U.S. v. Crescent Kelvan*, 164 F.2d 582 (1947), consents given, admissions, records, and other documentary evidence were admissible in criminal prosecution of the defendants. In *U.S. v. Stanack*, 387 F. 2d 849 (1967), both withdrawal of consent and refusal

of consent were viewed by the court as a prerogative of the defendants and necessitated a warrant.

A later case emphasizes the continuance of these circumstances in the case of the food and drug inspector. In *U.S. v. Thriftmart Inc.*, 429 F. 2d 1006, the 9th Circuit (California) upheld convictions of the managers of a supermarket food chain's warehouses that were based on evidence obtained during warrantless administrative searches of their premises by FDA inspectors. The inspections were routine and similar ones had been conducted periodically in the past. On arrival at the warehouses, the inspectors had approached the managers, filled out and presented their notices of inspection, requested permission to inspect, and in each case were told, "Go ahead" or words of similar import. The inspection notices contained a recitation of the applicable statute, which authorizes FDA inspectors to enter at reasonable times to inspect food warehouses. They did not have search warrants, nor did they advise the warehouse managers that they had a right to insist upon a search warrant.

The court of appeals affirmed the convictions, indicating:

... the administrative search is "neither evidence of crime" and this involves "a relatively limited invasion of the urban citizen's privacy." ... due to the public importance of the inspection process it should not be "hobbled by the blanket requirement of the safeguards necessary for a search of evidence of criminal acts." ... It is clear, therefore, that the administrative search is to be treated differently than the criminal search. ... In a criminal search the inherent coercion of the badge and the presence of armed police make it likely that the consent to a criminal search is not voluntary. ... These circumstances are not present in the administrative inspection. ... Nothing is to be gained by demanding a warrant except that the inspectors have been put to trouble—an unlikely aim for the businessman anxious for administrative good will. ...

We hold that the absence of coercive circumstances and the credibility of a consent given to an inspection justify a departure from the *Schoepflin/Schoepflin v. United States*, 391 F2d 390 (9th Cir.), cert denied, 393 U.S. 865 (1968) rule in cases of administrative inspection. ... In conclusion, we hold that in the context of the exclusionary rule a warrantless inspectorial search of business premises is reasonable when entry is gained not by force or misrepresentation, but is, with knowledge of its purpose, afforded by manifestation of assent. ... Advance notice of inspection under (the statute) is not necessary. ... FDA discretion whether to proceed criminally or civilly is constitutional; the FDA is not required to prosecute every violation. ... Nor need the FDA announce at the outset whether it wishes to proceed criminally or civilly. ...

The courts have a narrow scope of review of the FDA's action. This is true in the case of any administrative agency, notwithstanding that they are or are

not bound in their hearings and determinations by courtroom rules of evidence. Litigants challenging an agency's actions are not entitled to a complete rehearing on the factual and legal issues involved. They are more properly heard on new evidence not available at the time the administrative agency action was taken. Beyond that, the court must decide that the agency acted on substantial evidence, however obtained and weighted, and not in an arbitrary, capricious, and discriminatory manner.

In addition to such a narrow scope of review, the complainant faces the additional burden of overcoming the presumption of regularity afforded the acts of an administrator and other governmental personnel such as was enunciated by the court in *Pasadena Research Inc. v. U.S.*, 169F. 2d 375, *Citizens To Preserve v. Volpe*, 432 F. 2d 1307 (Tennessee) 1970. In the same way, courts will properly accord deference to an agency's interpretation of statutes and regulations which it administers, unless obviously erroneous, unreasonable, or inconsistent therewith. The court recognizes that administrative agencies have a primary task to administer broad policy mandates for the common good of our society and they cannot be required to refine their rules to assure tailor-made equity for each of the complexities that may arise. If they issue and interpret regulations that are rational and supportable in their general application, they cannot be charged with unreasonableness because in particular instances they may grind with a rough edge.

In 1970, however, the Court in *Colonnade Catering Corp. v. U.S.*, 397 U.S. 72, dealt with the statutory authorization for warrantless inspections of federally licensed dealers in alcoholic beverages. Federal inspectors, without a warrant and without the owner's permission, had forcibly entered the owner's locked store-room and seized bottles of liquor noncompliant with the tax and label sections of the pertinent law. The Court found for the owner, excluding the liquor bottles from evidence. They held that "Congress had not expressly provided for forcible entry in the absence of a warrant and had instead given the government agents a remedy by making it a criminal offense to refuse admission to the inspectors under 26 USC 7342." The Court thus indicated that in certain kinds of business or industry, closely identifiable with instant public endangerment, such as liquor, inspection and even unannounced inspection are basic needs for an effective system of controls. They further pointed out that in the context of a regulatory inspection system of business premises that is carefully limited in time, place, and scope, the legality of the search depends not on consent but on the authority of a valid statute.

In *U.S. v. Biswell*, 406 U.S. 311, the Court two years later had an opportunity to expand on "pervasively regulated businesses" directly associated with traditional and historic close governmental control such as alcohol and firearms. A similar statute as in the Colonnade case was involved, but here the inspection, although warrantless, was carried out without force. There was a valid underlying

statute that carried a right to inspect. It overlaid a traditionally pervasively regulated business associated with dangers of violence and crime to the public. The regulatee enjoyed federal favor in terms of his license or privilege to be in business.

Further, the Court differentiated the circumstances that caused warrantless searches to be prohibited in *See v. Seattle*.

In *See v. Seattle*, the mission of the inspection system was to discover and correct violations of the building code, conditions that were relatively difficult to conceal or correct in a short time. Periodic inspections sufficed and inspection warrants could be required and privacy given a measure of protection with little, if any, threat to the effectiveness of the inspection system there at issue . . . Here, if inspection is to be effective and serve as a credible deterrent, unannounced, even frequent, inspections are essential. The prerequisite of a warrant could easily frustrate inspection . . . When a dealer chooses to engage in this pervasively regulated business and to accept a federal license, he does so with the knowledge that his business records, firearms, . . . will be subject to effective inspections.

Following this case, many agency statutes were reexamined by the agency to determine whether they met the “warrantless inspection” prescription written by the Court in the *Biswell* case. Thus, the Occupational Safety and Health Administration (OSHA) argued eventually that its staff could enter the workplace anytime, any portion, in implementing its own highly pervasive statute. The FDA characterized the food and drug industries as pervasively regulated. However, the Supreme Court sounded a call to caution. Liquor and arms are special businesses and OSHA, which deals with no such special group, as pervasive as its controls might be on all its horizontal spectrum of regulatees, does not meet criteria of the *Biswell* case.

Many believe that the FDA, despite some few favorable lower court decisions, should look to the *Barlow* case rather than the *Biswell* case to measure its inspective authority. There are many analogies beyond the fact that most pharmaceutical plants must also consider OSHA. The law was held unconstitutional inasmuch as the *Barlow* case was not in such an exceptional business or industry and the statute purported to authorize inspection of business premises without warrant. The rule that warrantless searches are generally unreasonable applies to commercial premises as well as homes. *Camarra v. Municipal Court*, 387 U.S. 528; *See v. City of Seattle*, 387 U.S. 541, 87 S. Ct., 1737 (1967); note from the syllabus of the case as it appears in 98 S. Ct. on page 1818:

(e) Requiring a warrant for OSHA inspections does not mean that, as a practical matter, warrantless search provisions in other regulatory statutes are unconstitutional, as the reasonableness of those provisions depends upon the specific enforcement needs and privacy guarantees on each statute.

The inspection rights sought to be exercised by the federal agency were statutorily set forth as in countless other federal and state statutes.

Section 8(a) of the Occupational Safety and Health Act of 1970 (OSHA) empowers its agents: 29 USC 657 (2)

(1) to enter without delay and at reasonable times any factory, plant, establishment, construction site, or other area, workplace or environment where work is performed by an employee of an employer; and (2) to inspect and investigate during regular working hours and at other reasonable times, and within reasonable limits and in a reasonable manner, any such place of employment and all pertinent conditions, structures, machines, etc.

The regulations with respect to inspections, 29 CFR 1903, require an inspector to seek compulsory process if the regulatee demands same, or if partial or total access is refused.

Barlow's was an electrical and plumbing installation business, certainly not of Biswell character. The OSHA inspector, after entry to the customer service area of its enterprise (an area of invitation), presented his credentials to the proprietor and asked for entry to the working areas where he could conduct his inspection.

The inspector should seek and gain entry from one authorized to permit same. The proprietor, as in the Barlow case, was certainly appropriate. The time was reasonable; it was a time when the place was open for business. Inspectors for other agencies often show, in addition to credentials, an inspection form indicating that they are there to inspect pursuant to a statutory section. Whether they divulge their reasons for inspection is discretionary with them. While they are not likely to be untruthful, they may be evasive. The regulatee should always seek to ascertain the reason. Mr. Barlow did so here. In the case of OSHA, where complaints are frequently associated with employer–employee discord, the situation is particularly delicate on both sides. When Barlow asked whether there had been a complaint, the inspector replied negatively, but asked again to enter the nonpublic area of the business. Barlow said he could not unless he had a search warrant.

Regulatees often are willing to trade. The regulatee says, “If you will tell me what area of my activity is suspected of noncompliance, I will allow you access to it to show you that the report or rumor or complaint is wrong. If you won't be honest and cooperative with me, go get yourself a warrant.” The inspector replies, “That's not as good or fair a trade-off as it sounds. First, I may betray my source of information, which I was supposed to protect. Second, if I warn him and he feels in danger, he'll not let me inspect anyway. Third, if he's so protective there may be other troubles here I might observe.”

Does the case inhibit employee reports to OSHA? The opinion expressly says that it does not. It does say, however, “That an employee is free to report and the government free to use, any evidence of noncompliance with OSHA that

the employee observes, furnishes no justification for federal agents to enter a place of business from which the public is restricted and to conduct their own warrantless search.” Further, anything the inspector could have observed from the customer service area would have been admissible in evidence against the defendant.

If surprise searches have a reason for such and are contemplated, an administrative warrant can be secured, not only on specific evidence of an existing violation, but also on a showing that reasonable legislative or administrative standards for conducting an inspection are satisfied with respect to a particular establishment. The great majority of regulatees can be expected in normal course to consent to inspection without warrant. A warrant provides assurances from a neutral officer that the inspection is reasonable under the Constitution, is authorized by statute, and is pursuant to an administrative plan containing specific neutral criteria.

Among other issues raised by the government and dissenters was the mandate of OSHA to safeguard employees against hazards in work areas of businesses subject to the Occupational Health and Safety statute. These mandates have always enjoyed special status with the Court and are exceptions to the need for a warrant. Further, they say, to necessitate a warrant, the administrative warrant devoid of probable cause preconditions, is to dilute the warrant clause of the Fourth Amendment (5 to 3 decision).

In *Woods and Rhode Inc. v. Alaska*, Justice Rabinowitz writing for the Court, June 2, 1977, 565 P. 2nd 138, was in total agreement with the White opinion in the Camarra case and, had he but known, with the White opinion in the Barlow case as well.

Since the Supreme Court has emphasized in the Barlow case that an exception from the search warrant requirement may exist for industries with a compelling history of government oversight, and where no reasonable expectation of privacy could exist for a proprietor over the stock of such an enterprise, one can see that an agency may not wax confident that it falls within this narrow area of exception. The liquor and firearms industries comprise the exception, not the rule. The fact that a federal agency is granted governance over businesses involved in interstate commerce, alone, is insufficient to bring just any business or industry within such an exception.

In all of the Supreme Court inspection cases, the Court notes that the great majority of businessmen can be expected in normal course to consent to inspection without a warrant and the FDA will not be crippled as to effectiveness by providing those owners who wish to refuse an initial requested entry with a time lapse while the inspector obtains necessary legal process.

The Court in the Barlow case also indicated that requiring a warrant should not impose serious burdens on the inspection system or the courts because consent is the usual circumstance. Some government inspectors, however, demand that

the regulatee sign various documents authorizing the inspection and waiving rights, prior to commencement of the inspection.

For example, as to Controlled Substances, whether or not narcotic drugs, in 21 CFR 1316.06 through 1316.13 administrative inspections with and without warrant are described, and in conjunction with these, a printed form is provided the regulatee with instructions that it be signed. In the author's opinion (S. H. W.), the signature is not required to carry through a consensual inspection, and insistence by an inspector that the inspection will not be conducted without the signature is ill advised. To proceed to a magistrate for a warrant because the regulatee will only verbally consent to the inspection should be reserved for critical circumstances where criminal action is suspected on the part of the regulatee; otherwise, the judge is being abused by being troubled for naught.

In some instances, FDA inspectors, on being refused entry, have demanded that records be turned over to them for copy, notwithstanding. The Court indicated in the Barlow case that the inspection of the regulatee's documents, required to be maintained by the act and allocable regulations, may not be effected without a warrant, absent consent. Of course, the agency has subpoena power to force production of all such records.

Nothing said in defining the rights of inspectors and "inspecteds" is intended in any way to encourage the latter's taking a hostile, narrow, technical approach to the inspector's activities. Both, rather, should appreciate the mutual-ity of interest that applies: maintaining and delivering drugs of quality, of safety and efficacy, to the public. That is the mission of the inspector, and that is the only profitable way to stay in business. There is rarely an excuse for the inspector to be intrusive and the manufacturer to be obstructive.

When lawyers are asked for the legal determinants in a given situation, that is all they can supply as lawyers. Immediately following that, it becomes a policy decision for management. If they are not on good ground, then the delay they may gain may be less helpful than a sincere attempt at correction and remedy, for the FDA does have additional resources beyond Sections 703 and 704 of the act. There is a general acceptance and recognition that the regulations are sound and that necessary compliance with them is in the best interest of the industry and the public. With proprietary or prescription drug manufacturers especially, there is frequent misunderstanding between inspectors and proprietors because management policy may differ, because of personalities and the nature of trade secrets. When inspectors come to a manufacturing plant, they are looking for violations of the act and infractions of the regulations. They may come in to collect official samples, to copy documents showing interstate movement of a product (transportation record, the invoice, the bill), to get other information made available to them, and to learn what personnel can contribute most to evidentiary needs. Of course, sometimes their visit is the prelude to an establishment inspection.

From the standpoint of the inspected, it is good to know the purpose of an inspector's visit beyond the formal notice handed to the responsible plant official. Do not hesitate to ask this. Most inspectors will be responsive to the extent that they are permitted and circumstances allow. The question of whether they must advise you that they suspect a criminal violation of the statute and are seeking evidence accordingly is one that has been raised before the Court and not elicited any degree of support up to now. They may advise you that it is a routine inspection of your facility or some special part of function of your factory. In any event, besides a sit-down discussion of their findings or recommendations on leaving, they may make valuable suggestions during the course of the inspection, which means that someone capable of understanding the explanation should accompany them and make appropriate notes. As a matter of interest, especially for those unfamiliar with inspection procedures, the date, time, and description of inspection areas should be detailed, questions asked, answers given, and so forth, as well as identification of the inspectors—all on a report for the manufacturer's interest and assistance.

By virtue of their authority, inspectors can ask for legend drug products in their packaged preshipment state. If asked, the inspector will pay for them at a determined price. In such instance, or if the manufacturer does not wish to make a charge, the manufacturer usually exchanges an invoice for a receipt, noting the exact facts of the distribution. Of course, here, as wherever the FDA takes a sample, duplicate equivalent packages from the same lot should be set aside for future comparative analytical needs, some portion of which should be checked by quality control immediately to assure being able to react quickly if necessary.

Inspectors who want a line sample are generally willing to await a convenient point in the processing to either merely observe or check it, or withdraw it for further action. Any such sample should be marked appropriately and receipted with the acknowledgment that it is from unreleased stock. Again, an equivalent sample taken from the same batch should be withdrawn by the manufacturer's quality control unit for immediate and later comparative analysis. What the manufacturer reserves as its own contemporary samples should be stored under appropriate and recommended conditions.

If inspectors unknowingly breach a sterile or other "untouchable" proceeding, they should be so informed and the material involved rejected with reason given in the record, as always in the case of rejected materials. Needless to say, if the inspector is about to unknowingly breach it, stop the inspector and explain.

Inspectors are given specific instructions and are quite expert at handling various types of samples. This in a sense involves their own quality control. The manufacturer, therefore, should always note, perhaps on a receipt for the sample and not necessarily over the inspector's signature, the manner in which the sample was taken and transported.

Again, to use an obvious example, the inspector knows better, but if he or she puts a few vials of one of the nitrate preparations in a glassine envelope and slips it into a breast pocket, those tablets may not do so well on final assay some hot hours later.

Experienced counsel in this field frequently advise clients that since seizures are in rem proceedings, they are better off, for many reasons, immediately destroying goods where question of adulteration and/or misbranding arises, and the value is less than some given figure. They should, of course, then record this for tax purposes also. In a sense this is associated with the FDA recall technique, for many of the same reasons.

There are aggravated situations where attorneys tell their clients to answer no questions except those that are submitted to them in writing and signed by the interrogator with a statement of authority; to satisfy no requests for samples or copies of records except where request for same is similarly submitted in writing and signed by the interrogator with a statement of authority. This is really dealing at arm's length.

In enacting additional factory inspection legislation in the field of prescription drugs, Congress did strengthen the FDA procedures on new drug product licensing, as some regard it, and did broadly increase the subject matter of inspection to include research data, quality control information, complaint files, and so forth. It did not establish continuous factory inspection as a requirement, nor did it apply these broader inspectional prerogatives to other drugs. There is still no section of statute that makes a recall mandatory. Recalls are undertaken to retrieve from the market drug lots that fail to meet regulatory requirements. As a matter of fact, HR 6788-S.2580 (1964), which sought to expand inspection authority, as currently for prescription drugs, to foods, OTC drugs, devices, and cosmetics, by adding a subpoena section to the act, was never passed. However, device inspection has been enhanced by the Medical Devices Amendment. In some ways device inspections for "prescription devices" exceed those for drugs.

There are occasions when the inspector feels a picture is worth a thousand words. The inspector will take photographs. These could be a floor or room condition that shows failure to segregate, or poor sanitation, personnel failures, poor security arrangements, or poor equipment, and so on. Since the FDA regards photography as adjunctive to inspection, they will only infrequently ask first. There is no denying, however, that this aspect of inspection is arguable and, therefore, capable of reasonable mutual satisfaction. In some instances, therefore, either the manufacturer takes the picture designated by the inspector exactly as the latter wants it done, and also retains a copy, or pictures are taken separately and simultaneously along with the inspector, covering the same angle and materials. There are instances where the proprietor refuses to allow photographs to be taken and refuses to provide them on constitutional grounds or for protection of trade secrets. Relying upon the Dow decision, the FDA is aggressive regarding

their right to photograph in an inspection. Their faith in Dow may, however, be misplaced. The particular circumstances of the case and the need for aerial photography shown by the FDA is not really analogized to the ordinary pharmaceutical manufacturing plant.

Other problems remain in the FDA inspection area. Can the FDA take photographs without permission? Must the FDA warn the persons inspected that they are seeking evidence for criminal charges? Is it doubtful that there is any more authority for a right to photograph a premise than there is to conduct a warrantless search? Consents are not eternal. On the other hand, the Miranda case warnings are not required in an FDA inspection because it takes on a premise that remains under the control of the proprietor.

For the same reason, a mere statement of objection to FDA photography will not suffice to challenge the admissibility of the photos later. In order to accomplish that, the proprietor must order the FDA inspector to leave his camera behind and not take pictures. Then, if the inspector takes them surreptitiously rather than by procuring a warrant to inspect by such means, the photographs could be excluded.

HOW EXPERIENCED INSPECTORS USUALLY CONDUCT THE INSPECTION

The inspector will pull the file at his or her office on the factory or establishment in question and see how it fared in prior inspections, how it stands as to recall records or even past or pending litigation with FDA. If there have been recalls, whatever follow-up was made, what reasons were given and/or found that caused the recall are worth reconsideration preceding the inspection. Certainly, if samples had been collected directly or indirectly under this factory's label, analytical results on these samples would be reviewed.

The prior inspection observations will have been prepared by the FDA representative who had previously inspected the plant. As part of that report, the section captioned "Discussion With Management" offers a considerable insight to management's attitude, capability, and willingness to be remedially responsive. The inspector will, in this inspection, want to compare the List of Inspectional Observations with what was done by management to correct them.

Following this review, and in the course of the factory's normal working hours, thus generally between 9 a.m. and 5 p.m. on a weekday, the inspector will present himself or herself, display credentials,* and issue a Notice of Inspection.

* Bearing the inspector's photograph, seal of the department, and enumeration of authority, as described previously.

The Notice, of course, draws attention to the fact that inspections have a firm legal basis in the Act. The Notice is not to be confused with an administrative search warrant or summons or subpoena.

At this point, since the inspector is at the office, it's usual for the inspector to ask for any changes in the name, corporate status or officers, and the areas of responsibilities for each if they are separate.

The same kind of update may be requested as to products newly undertaken, or deleted (and why). It is usual for the proprietor to set someone in accompaniment of the inspector, and usually this person will acquaint the inspector quickly with new procedures, new policies, and new equipment that will enhance productivity and quality assurance. In fact, frequently it is a member of the regulatee's quality control staff who undertakes this duty. There are advantages in having one or two persons consistently undertake this assignment, since they develop "carryover," rapport and a technique of question and answer, mutually profitable to the agent and the regulatee. The disadvantage is the loss of such continuity through absence, but perhaps more importantly, the narrowing of communication of the inspector's concerns and observations.

The usual inspection will start in the receival area, and the condition, security, and cover of the unloading dock may capsule all subsequent findings. Someone who is careless at that point, who provides no shelter from the elements for articles being unloaded, is going to show carelessness elsewhere in the inspection. From that area and a study of the receival book with neat inked entries that provide an insight into the history of all articles received, and that can be used to trace the course of an ingredient or a container to the finished, packaged, shipped dosage form, the inspector's trail will usually go to storage. The key to storage observation that will meet the inspector's approval is segregation of materials in ways, standard or innovative, that actually preclude commingling of dissimilar substances, or dissimilar forms of substances, or dissimilar chronological groupings within the same substances.

Sanitary consideration in storing, as well as security, will be a concern. How high a stack? How far off the floor a skid? Why is this article stacked on the floor without a skid? Condition of new materials, and appropriateness of containers, temperature, and humidity are noticed.

Segregation of released from unreleased materials, of goods ready for shipment from goods returned, is also seen.

Even as the receival area was observed for its room, condition, and coverage, all of the plant space will be similarly observed and analyzed by the inspector for its safety and adequacy for purpose. He or she will look for space as an indication to the presence of available segregation between operations to prevent mix-ups.

Thus, the inspector will look for the quarantine area in terms of size, location, and manner in which quarantined items are signally labeled. To prevent

potential accidents through lack of information, is the quarantine situation set down in writing? How about the plan for sampling from the materials? Is there a written plan that tells the number of containers in the lot from which a sample is to be taken? The inspector will want to observe any sampling operations that may be in progress. By the way, the inspector will examine all of the implements and containers used by the samplers, for cleanliness and suitability. Unclean or reactive implements are obvious adulterants.

Then taking some one of the raw materials, a suspect one, if that has already come up, or any one otherwise, the inspector will follow that to the production area.

In the production area, the inspector will be alert to product, personnel, and equipment, as well as the production environment. As to the latter, the inspector will look to facilities for sanitation, proper light, air, water, and cleanliness of general and specific production areas.

The inspector may be expected to examine all of the equipment in the production area to determine that every surface that meets with ingredients, immediately completed or completed dosage forms, is nonreactive.

Every major piece of equipment that is fixed to the room, along with mobile equipment that is moved from area to area as needed, should be lettered or numbered and as so identified, appear in the proper place on the batch record.

Not only should it be clean for use, but its cleaning and maintenance record should be handy for inspection. The inspector, based on experience in other establishments, may not only check as to the procedures used in cleaning, maintenance, calibration, etc., but may suggest improvements in frequency and technique. The inspector will look for drains for washability, and in the drains for product. In the latter instance, the inspector will consider discrepancies and carelessness in reconciliation of production figures. He or she will look for screening, methods used for extermination, the freshness of paint and its condition, telltale spots that indicate environmental nonintegrity for the product.

Expect the inspector to ask as a primary question in the production area: "Where is the batch record for the product that you're working on?" In the light of the CGMP regulations, the inspector is entitled to see that for any drug, old or new, Rx or OTC. He will check immediately against it the present stage of the processing to assure that the recorded activities are truly contemporary. He may quickly "back check" to assure the preparation up to this processing point. In the original Willig-Tuckerman manual, the concept of "doers" and "checkers," since adopted by the federal regulations, was first established as an element of current manufacturing care. The inspector follows that guide. For example, if components are being weighed out, the inspector will look for two sets of initials on the batch record. This will show someone weighed, someone checked. Initialing omitted or preinserted is an indication of an operation that is high on formalities but low on care.

The inspector will usually run a quick check of the calculations on the batch record at that point also. The batch record itself, by the way, should also have a signature and date showing that it is an accurate photocopy or other reproduction of the correct master formula record.

Of course, the inspector will continue the course of the raw materials, now the product, in terms of the formulation, the batch record, the theoretical and actual yield, and the sensory impression of the finished product, along to the packaging.

Here many of the same observations will be sought, but special emphasis will be placed on the componential check of the packaging assembly. Are they doing the specified packaging? What kinds of assurance have they as to its identity, quantity, and quality? What is the appearance, the experience, the education of the personnel involved, and are there enough people to carry out necessary job assignments? Is the health and maintenance of the employees of such nature to contribute to manufacturing safe and unadulterated articles?

Looking carefully at the production and packaging equipment for cleanliness, appropriateness, lubrication, use according to manuals, maintenance generally, the inspection can actually gauge the character of the production management.

As to equipment, inspectors are certainly impressed by quality, newness, size. However, they will be looking for makeshift innovations to equipment usually applied by an operator and without management's knowledge. The operator sees the flow of finished tablets pile up as they come through the stainless steel chute of the machinery, so pastes in a separation or diverter that doesn't come out, isn't cleaned, etc. The operator operates at higher speed by adding improper lubricants.

At every stage in the handling of the equipment, the inspector will be looking also to the initials, the dates, of "doers" and "checkers."

The inspector will look for the chronologic and actual gap between completion of packaging and shipment. There must be some holding area or special warehouse at which such products will be kept quarantined until the quality control personnel have had a chance to check their results and give releases. In the case of controlled substances, there are extra considerations of which an FDA inspector will be aware, but which are more likely to be checked by state and Drug Enforcement Administration (DEA) officers. That is the question of accountability for finished goods tested by quality control and continuing security for the quarantined materials.

Similarly, with a view to continuing security in the case of controlled substances and in all cases with a review of procedures that move the finished product from the holding area to the finished goods (released for sale), shipment for sale area, the inspector will continue observation of product flow to the exit. Although the regulatory effects of the CGMPs have, for varied reasons, deemphasized the importance attached to proof of interstate commerce, both inspectors and those

inspected realize that articles segregated for filling a shipping order are held to be constructively in interstate commerce even though they have not yet been placed in the carrier. The inspector will, therefore, not only observe the personnel and the manner in which they conduct themselves in this “exit” stage, but will also look for the same care and cover in protection and handling of articles earmarked for shipment, as looked for previously. It is not very sensible to exert much care in the manufacture of the product and then leave it to stand for an inordinate period, in an improper climate, exposed to elements and insecurity. The inspector will also be looking at paper, at distribution record keeping, at accompanying invoices. For purposes of recall, the inspector will want to see that the distributor has recorded the customer’s name, address, registry number if applicable, date, quantity of identified articles shipped, and the control or lot number thereof. The inspector will ascertain that they know and understand the 2-year record holding time requirements. The inspector will, no doubt, tie this in with a check into record keeping for products shipped out with an expiration date. The CGMPs call for records to be available for a period of time beyond that expiration date.

Having reached this point, and given sufficient time, the inspector can be expected to backtrack. Taking note of some article in the released area, he or she may go back to quality control, present them with the identification of the article including the lot number, and ask to see all the analytical data relating to the testing and release of the particular lot.

Checking the findings against the acceptance specifications established by the manufacturer or compendially for the article is an obvious opportunity to check on acceptability.

If some question exists or has been raised with the inspector previously as to verity, he or she may ask for the analyst’s notebook, the raw data, and relate this to the figures provided. A look at the reviewer’s signature or initials as well as those of different analysts who may have carried through various tests will provide the inspector with a reference point for further discussion if needed. The reviewing inspector will not only look to results of testing, but will also look to methods used in testing for identity, stability, etc. While compendial tests are important for legal purposes, use by a manufacturer of other methods, including some that may be shorter or less expensive, but not as reliable, and failures in validation records will alert the inspector to different degrees of care. Similarly, for those products with established expiration dates, the inspector will want to see data indicating that adequate tests are being performed on products actually retained for the length of the expiration date’s time period. It is an undesirable short cut to base such data and findings on accelerated and otherwise contrived aging of the article, instead of on the product actually aged.

Certainly, the nature of the products, including their physical characteristics, may predetermine the kind of quality control equipment and methodology

to be employed, but each inspector has a capacity to compare what one firm has and does by what number and quality of personnel, as it compares to another with a similar product output.

Again, usually close to the “exit” time in the traditional general inspection, the inspector will request a review of the manufacturer’s complaint files. He or she may ask to see all those with respect to a particular product, from a particular date. The inspector is more apt to get cooperation in the latter request. Complaint files are required to be kept and maintained for all drug products under present CGMPs. However, especially for OTC drugs and cosmetics, actual access to them is not as clearly granted by the federal inspection laws. Among many larger producers, they are not kept in the manufacturing facility. The inspector is, however, clearly authorized to ascertain that the file exists and is maintained. Since the file can be opened for study by administrative subpoena, withholding free access to it may only gain time and principle for the regulatee, and that carries its own costs. Therefore, if the inspector requests, with particularity, he or she is not considered to be on a fishing expedition that may involve a look at complaints not within the FDA’s primary concern, and will probably be shown that which he or she seeks.

COMPLAINTS

In examining the record keeping of the company or other distributor with respect to complaints, inspectors may remind them that the current good manufacturing practices require that the manufacturing firm shall maintain a record of all complaints, whether they are received in written form or orally communicated from some other source to the manufacturer. They are also bound to make an investigation of each complaint, and a record should be kept showing the results of that investigation. Of special interest to an inspector are those complaints that might indicate a formulation problem or some problem derivative of the product labeling and even those that might indicate unusual stability or decomposition. As a minimum, the company on receipt of a complaint should be able to show that it has examined reserve portions of the lot in question if it has been identified by the complainant, and if it has not been identified by the complainant, the company should be able to show that it has compared the complaint for the possibility of receipt of prior complaints on the same or related score. In any event, complaints of a medical nature are expected to be followed up in a great deal more depth. An appropriate evaluation of the complaint should be made by a physician on behalf of the complainant or the company, and perhaps both, and such reports should be in the file. Needless to say, it would be anticipated that in most instances an adverse action report would have been sent to the FDA and a copy of same would appear in the complaint file for the particular product.

One of the salutary changes in inspector and “inspected” relationships has been the growth of the mutual recognition of responsibility. Therefore, upon the completion of the inspection the inspector will want to contact responsible management and officials. He or she will certainly desire to have top management “prepped” where there are important problems in the area of adulteration or misbranding that will require considerable investment in personnel, equipment, and remedial pressure to correct. Sometimes management may represent various areas of the company structure. There may be different personnel there who head production and quality control. Certainly the inspector wishes to be assured that responsible officials will be there to receive comments. It is at this time that the inspector will issue to them a list of the inspectional observations and discuss each point separately. The inspector will probably elaborate upon the circumstances under which the observation has been made, including references to named personnel who witnessed the activity. The inspector may take this opportunity to acknowledge corrections that were made at the time or welcome the opportunity to hear about corrections that may have been made subsequent to the observation. He or she will then ask for commentary from the management personnel present, to determine essentially in advance what their attitude will be. In short, do they intend to disagree with the findings and are they disturbed by the thought that changes will have to be made? Or, and of course this is preferable for the inspector, are they more apt to agree with the findings, even though they may offer explanations in mitigation of such findings, but yet acknowledge the need to improve and correct the situation. The inspector should always ask, and generally does, for a complete correction rather than a modification. The goal should be to educate for voluntary compliance, and at the same time to deter a repetitive violation. The inspector will, of course, carefully note the responses that are made to this presentation and incorporate specific quotations, as well as the general tenor of the response, within his or her report for each point made in the list. That essentially is a basic approach that the inspector will use for the average manufacturer of drug articles.

Very frequently inspectors are called to investigate problems that are suspected as to various firms involved in the manufacture, distribution, and holding of prescription and over-the-counter drugs. One such issue will occur as a follow-up to a consumer or competitor complaint. While the inspector will generally not release the name and address of the person who has complained to the FDA unless the inspector has received authorization to do so, he or she will seek to provide as detailed information as possible to the firm so it can really make a significant follow-up. Therefore, the inspector will try to determine from the consumer or competitor complaint what product or lot is involved rather than seeking to simply be concerned with every product or every lot, no matter what lot or control unit it was based upon. Certainly the inspector will want to know whether the firm has received prior complaints on a certain product with that certain lot

number. It is not surprising that in many instances the manufacturer has already been made aware of the complaint. The complaint may have followed a correspondence between the buyer and the manufacturer in which the buyer had asked for replacement expenses, or even medical expenses. In such a situation, often the inspector can proceed with work and review of what the manufacturer has already begun. In visiting the plant where a physical defect has been involved, the inspector may be expected to request a reserve sample from that lot to examine it for the defects that had been noted. The inspector will, of course, want to see the complaint file for that product, to see on a quantitative basis what involvement with similar problems has occurred. The incidence of complaints compared to the incidence of sale will provide a realistic ratio of concern when measured within a defined time period. However, this type of approach will not exclude the possibility that the public may be endangered. (For example, there is the classic case of the manufacturer who had sold millions of jars of product and noted only 40 or 50 complaints. Subsequent litigation indicated that the manufacturer had failed to sufficiently warn users.) Therefore, even where incidence is fairly small the inspector must realize the misbranding potential, just as the manufacturer must recognize the product's liability potential.

Where there have been complaints of an adverse reaction or some other serious medical injury, the inspector will want to be able to contact all those involved in the initial prescription or dispensing of the drug, as well as those who examined and treated that person subsequently. If hospital records are available because the patient had emergency or other hospital treatment, these should be made available to the inspector. The individual who has complained has of course released for disclosure such information that might otherwise be deemed of a confidential, and therefore restrictive, nature. If the reaction has been alarming and significant in that it either quantitatively or qualitatively exceeded the kinds of reactions that appeared in that company's labeling, the firm should have notified the FDA with the promptitude required by the new drug reporting regulations found in 21 CFR 312.1 et seq.

The inspector should attempt to collect samples from the same lot of the product that has caused the complaint, if such is available in the plant warehouse. In some occasions it may be necessary to purchase a sample from that lot from the retail establishment that provided it for the complainant. Another help along these lines will be the distribution record of the manufacturer, which may indicate the distribution of that lot and enable the inspector, either alone or with the cooperation of other inspectors, to collect a sample from that lot in some other outlet in that distribution scheme. If the matter warrants an extreme measure, the FDA may request a portion of the retention sample that was kept by the firm for its own testing purposes, or the FDA may request a portion of the sample that was perhaps provided by the complainant. Should the complaint seem both genuine and ominous, it may be anticipated that the FDA will start to look closely at

similar drugs made by the same manufacturer or other manufacturers that use the active ingredient that seems responsible in the complaint.

A classic case, in which FDA inspectors found that a children's aspirin had become contaminated with diethylstilbestrol, which caused engorgement of the breasts of the children using those tablets, has led to a general care on the inspector's part to determine what contaminants may have been involved in the manufacturing process of a drug that is the subject of a complaint. For example, an untoward allergic reaction from a drug that has no past history of such may be entirely due to the fact that the patient suffers from a penicillin allergy and there is penicillin contamination in the plant. The inspector therefore will press to examine the manufacturing logs to find out what products were made, perhaps on the same equipment, previously or on adjacent machines during the same processing times.

There are other situations in which the inspector may be called on to initiate an intensified inspection limited solely to determining the cause of the complaint with that product. In the event the complaint was due to mislabeling, as where the product was labeled with the name of another drug or with the wrong quantitative declaration, an in-depth review should be taken of the entire packaging and labeling operation in that plant that might be responsible for such a mix-up.

WARNING AS TO PREAPPROVAL INSPECTIONS

In the course of the PAI, those inspected should recall that the policy of the FDA will consider criteria of importance to pharmaceutical manufacturers. If a company has attempted to subvert the integrity of the FDA's evaluation or review process through acts such as offering fraudulent submissions, bribes, or illegal gratuities, the agency must take steps to assess the integrity of the firm's marketed products as well as the data and information provided by that company in support of products submitted for approval. In such cases, the agency intends to conduct an investigation and audit to establish the extent to which the firm's illegal or unethical behavior may have affected approved or pending applications. The scope of such an investigation will be determined by the nature of the offense and will focus on the reliability of research and manufacturing information.

To approve an application, FDA must determine that the applicant is capable of producing a safe and, in the case of some types of applications, effective product based on, among other things: (1) testing and other data provided by the applicant and (2) the adequacy of the applicant's manufacturing processes and controls. A key element in making this determination is the reliability of data and information in the application.

When the FDA finds that the data in the application are fraudulent, the agency intends ordinarily to refuse to approve the application (in the case of a

pending application) or to proceed to withdraw approval (in the case of an approved application), regardless of whether the applicant attempts to correct the falsification with a new submission in the form of an amendment or supplemental application. Thus, should the applicant wish to replace the false data with a new submission, the new submission must be in the form of a new application. The new application should identify the parts of the original application that were found to be false, and the accuracy of the application should be certified by the president, chief executive officer, or other most responsible for the firm's operation.

The FDA may also seek recalls of marketed products and request new testing of critical products. In the area of pharmaceuticals, for example, this would include products that are difficult to manufacture or that have narrow therapeutic ranges. The agency may pursue other actions under the FD&C Act or other applicable acts, including seizure, injunction, and criminal prosecution as necessary and appropriate.

Firms engaging in fraud, material false statements, bribery, or proffering illegal gratuities will ordinarily need to take the following corrective actions to establish the reliability of data and information submitted to the FDA in support of pending applications, and to support the integrity of products on the market:

1. Cooperate fully with FDA and other federal investigations to determine the cause and scope of any improprieties or problems related to safety, efficacy, or quality of products.
2. Identify all individuals involved in committing, or who are otherwise culpable in, the improper acts, or who have been convicted of an FD&C act or related violation, and ensure that they are removed from any substantive authority on matters under the jurisdiction of the FDA.
3. Conduct a credible internal review in order to identify all instances of fraud, false information, or any other discrepancy in applications submitted to the agency or between conditions of approved applications and actual production. This review should involve an outside consultant who is qualified by training and experience to conduct such a review, and the results must be made available to FDA for independent verification. Such a review is intended to supplement the agency's ongoing comprehensive investigation to identify all instances of fraud and other improper conduct.
4. Commit, in writing, to an operating plan to assure the quality, safety, and integrity of its products. Such a commitment will ordinarily be in the form of a consent decree or agreement signed by the chief executive officer and submitted to the FDA. Such a plan will, as appropriate, address procedures to preclude future instances of fraud and noncompliance with regulatory requirements for approved applications as well

as procedures to preclude any recurrence of other violations that may have been found (e.g., a comprehensive ethics program).

The FDA intends to inspect the firm and must be satisfied that the audit has been satisfactorily completed and that the firm's written plan has been satisfactorily implemented. Such inspections should disclose positive evidence (e.g., effective management controls, standard operating procedures, and corroborating documentation) that the firm's records are reliable and that the firm can be expected to manufacture products in compliance with CGMP and application requirements.

The firm may also be requested under existing regulatory procedures to recall products affected by false information or that otherwise lack adequate assurance of safety of quality. In addition, it may be requested to commit in writing to such retesting of any products (including, in the case of drugs, bioequivalence–bioavailability retesting) as the FDA may call for.

PRODUCT LIABILITY

With the burgeoning worldwide expansion of product liability litigation has come another force to add significance to establishment and maintenance of CGMP.

Through broadly permitted discovery procedures, today's manufacturer is subject to review by other than governmental personnel. Frequently adversaries in litigation seeking to substantiate claims based on alleged defective products use the services of persons expert and conversant with CGMP in the hope of finding tangible evidence of such manufacturing or quality control features as would cause the product to be defective and dangerous to the consumer. This is especially true in the case of biological drugs, vaccines, medical devices, and their components. Thus, there exists a strong economic and potentially debilitating force to wreak havoc upon the careless or the unconscionable.

SPECIAL PROBLEMS ENCOUNTERED BY INSPECTORS

- After the inspector arrives, he or she is told to come back another time because the person in charge, or owner or operator is not at present there. Besides the obvious comment that any plant or facility in operation must be under supervisory guidance, the agent will ordinarily firmly advise that the person in charge is expected to permit the inspection, that whoever is refusing in the name of the proprietor may call counsel or owner or anyone else for advice in the matter, and that a

refusal of entry will be noted whether or not that refusal is by a manager, owner, or other in charge.

- After the inspector arrives, he or she is advised to accompany a person delegated by management. This does not mean the inspector is to go on a tour. It means the inspector will go about the inspection, starting at the point deemed necessary, and that the facility person will accompany the inspector.
- After the inspector arrives, he or she is kept waiting an inordinately long time. That is both discourteous and mutually unproductive. The regulatee should be advised, after a reasonable time, that the inspector will note it as a refusal of entry.
- After the inspector arrives, he or she is advised that there are no prescription drugs made there and therefore the inspection should be limited. While it is true that Section 704 expresses, by reciprocal observation, that certain limitations exist since the special prerogatives as to prescription drugs are set out, the area is not clearly a group of “do’s” and don’ts.’’

Whether the establishment does or does not handle Rx items, the inspectional procedure is fortified for both OTC and Rx articles, since the Current Good Manufacturing Practices apply equally to both. Extended as this now is for devices, and likely to extend to cosmetics in the future, one can see that inspectors have procedural guidelines for many articles, to determine whether the processes, facilities, and controls conform to the regulations. However, if a manufacturer declines to show the inspector the formula records for an OTC product, the manufacturer is doing that which is a legal entitlement under the law. The manufacturer may thus likewise refuse to allow copying of a formula for an OTC. Yet, a compromise can be reached where the inspector for CGMP purposes will be allowed to compare master formula records against corresponding batch records and finished products labeling, for errors in transcription, clarity of photocopy or other reproduction used by the plant, accuracy of calculations in transposition, and completeness of label information as stated in the CGMPs. Some means to compare actual to theoretical yields and to explore discrepancies is necessary for Rx drugs, OTCs, and new and old drugs.

- After the inspector has arrived and commenced the inspection, the regulatee refuses to allow access to particular areas or files or documents. That is viewed as a partial refusal at the least, but the reasonable inspector will neither threaten nor haggle. The inspector will go ahead with the balance of the inspection and describe and incorporate the circumstances of the denial to his or her supervisor. After that, the office will decide whether it needed that which was denied, and usually an administrative warrant will be then obtained. Sometimes a phone call may

make that unnecessary, but officials feel it is best to procure the warrant and use it when a second chance at voluntary access is refused. For many reasons, the inspector will prefer to gain access without a warrant. This can obviate later admissibility problems. But it must be voluntary, rather than coerced or misled. It is conceivable that refusal to permit entry for inspection may be prosecuted criminally, but that does not mandate inspection. In usual practice, on federal and state level, the refusal is followed by obtaining a warrant, and is added to whatever charges arise from the inspection subsequent to the warrant.

Warrants can, of course, be challenged on diverse legal grounds, and that is true of administrative warrants also, but to a far lesser extent.

When a regulatee refuses to honor a warrant, that becomes a singular contemptuous act and makes the regulatee subject to swift punishment on that basis alone. However, inspectors should give the regulatee an opportunity to check with counsel or the home office or any other advisor prior to deeming the warrant dishonored.

GMP INSPECTION: PRACTICAL CONSIDERATIONS

Some of the legal issues associated with an FDA inspection have been addressed. In this section some key practical points will be presented.

First, it should be accepted that the FDA inspection does provide a useful independent review of plant GMP activities. In an effectively managed plant, self-audit and QA audit (see Chapter 7) should have identified any significant shortfalls with respect to systems and compliance and have resulted in correction. The FDA inspection should not therefore identify any unknown deviations; if it does, management needs to relook at the way it operates and not just respond to any citations.

It also should be acknowledged that the FDA inspector is only doing a job and that a constructive working relationship should be more productive to both the FDA and the company. On arrival at the plant the inspector should be asked to confirm his or her identity and be introduced to the key plant personnel. Any specific interests of the inspector should be identified and also the anticipated duration of the inspection. An ongoing straightforward relationship will facilitate this. These points allow management to program their time and, where appropriate, production operations, to better meet the requirements of the inspector and to minimize business disruption due to the involvement of managers in the inspection.

It is recommended that one individual be designated to lead the inspection on behalf of the company. This individual can significantly influence the tone of

the inspection and the opinion of the inspector about the company's attitude to CGMP compliance. The designated individual must be knowledgeable on:

1. CGMP regulations
2. Previous FDA inspections
3. Company policies and procedures
4. Detailed operation of the facility
5. Key people within the facility
6. Quality issues over the past two years (statutory inspection frequency is every two years) but plant inspections may have been more frequent. That is usually a warning they will continue to be more frequent.
7. Any ongoing atypical activities in the facility—upgrading, expanding, decorating, new equipment.

The designated person should:

1. Accompany the inspector at all times and act, where necessary, as an intermediary in the clarification of questions and answers. A “don't know” answer is preferable when there is uncertainty, provided there is follow up to obtain an answer in a timely manner.
2. Make notes of all points raised by the inspector regardless of whether or not they are likely to appear in the inspector's written report or to result in a citation. These notes can form a useful basis
 - for daily review with senior plant management.
 - for identification of points requiring immediate action; this also demonstrates commitment to the inspector
 - to highlight points requiring further elaboration or clarification with the inspector.
 - to integrate into a composite action plan after the inspection
3. Coordinate the assembly of requested documentation.
4. Notify the inspector of any company policies that impact on the inspection, such as the wearing of protective clothing, medical screening before entering the sterile suite, taking of photographs.

An FDA inspection ends with an exit interview where the inspector presents comments and, where necessary, issues an FDA 483 identifying observed deviations from the CGMP regulations. The exit interview provides a further opportunity to clarify any misunderstandings or misinterpretations. In many instances an inspector is prepared to take the comments from the exit interview into account when drafting the FDA 483. Any actions already implemented would be noted at this time. Since any proposed deviation may be invalid following retrospective review, the exit interviewee should be courteous, not adversarial, but not necessarily apologetic or a “breast beater.” Give the inspector every indication that careful review will be made of the helpful observations.

After departure of the inspector, management should review the overall impact of the inspection, not just the FDA 483 citations. Programs should be initiated to identify the basic causes of any FDA-noted deviations that stand up after internal review, and actions should be promptly implemented to correct these causes. Many, if not most, deviations are caused by inadequate attention from management and supervision, which sends mixed signals to other employees.

Most companies prepare a formal response to an FDA 483. This is an important document with possibly far-reaching results and implications; therefore, it should be done with care and foresight. This will indicate any corrective actions being taken, usually with defined time frames. Where management do not agree with a citation they should provide comprehensive reasons for the disagreement. When the FDA inspection is a Pre-Approval Inspection (see Chapter 19), this approach may need to be modified. Such disagreements have frequently resulted in recommendations to not approve the applications (NDA, ANDA, Supplement). In these circumstances the potential adverse business impact on the decision has “encouraged” companies to accept the FDA citation and to “implement appropriate, and sometimes unjustifiable actions.” Unfortunately this can then create the position that this is now considered by the FDA to be “Current GMP.” Regardless of this stressed situation, companies should continue to apply sound science and professionalism in the interpretation and compliance with the CGMPs. Every citation point should be addressed. In drafting the response, it should be remembered that it will be read by the inspector’s supervisor and consequently sufficient detail should be included to allow the supervisor to clearly understand the response. A useful approach is to have the draft plant response reviewed by a function or functions outside of the plant—such as Group or Corporate. This tends to ensure greater clarity. The response will take some time to assemble if it is to include time scales for actions. However, the speed of response also sends signals to the FDA that indicate the company’s attitude to quality; consequently the response should be seen as a high-priority item. In the event of a potential delay in responding it may be advisable to indicate this to the FDA, along with the reason.

There has been a considerable difference between the intensity of inspections in the United States and those performed by the FDA in other countries. This was primarily due to the lack of resources—financial and personnel. Domestic inspections could frequently involve more than 20 “person days,” while foreign inspections rarely exceeded a few days. In recent years the FDA has borrowed domestic investigators for foreign inspections and this has helped alleviate the people problem. While a few foreign inspections have extended to about 10 days, there still exists a major difference. Under normal circumstances it should be possible with an inspection of 5–10 days to ascertain whether a facility is in a general state of compliance. Longer that this really is a hunt to find deviations.

Currently FDA investigator performance evaluation appears to be based on the number of violations cited. In 1996 the FDA intends to move its emphasis toward compliance problem solving in a collaborative mode. If this occurs, then we can expect to see a healthy interactive environment in which quality, efficacy, and efficiency will all improve.

In 1994 the Office of the U.S. Trade Representative and the Department of Commerce initiated discussions with the European Union (EU) on the subject of mutual recognition of inspections. Initial progress was slow, largely because of the differences in inspections between EU member states. However, discussions are continuing with the FDA requiring equivalence between the EU member states and the FDA, the right to inspect, periodic joint audits, and access to EU inspection reports. Work will also continue toward harmonization of GMPs, but not through the auspices of ICH.

In addition to the exit interview and the FDA 483 (where issued), the inspector writes a comprehensive report of the inspection, the Establishment Inspection Report (EIR), which includes formal data on the company and its organization, points noted during the inspection, including those not appearing on a Form 483, and usually opinions on the attitudes of the plant personnel. Copies of an EIR are available through Freedom of Information.

Occasionally, proprietors suspect that inspections may be a cooperative enterprise between federal agencies, whether on an institutional or individual agent basis. There are interesting overlaps, for example, between OSHA and FDA inspections, and the comparatively newer inspection techniques of the former go somewhat beyond the latter. Photography and videotaping, use of employees to wear sampling devices, etc. are more frequent in areas of OSHA activities, and have been upheld by the courts.

The impropriety of having inspectors for one agency inspect and report to another have been discussed in the past, and there is a substantial basis for suspicion of such conduct, the regulatee should consult with counsel for his or her association, or his or her own counsel, promptly.

For the reader's interest, see the suggested preparation for and management of an OSHA inspection. See also the Barlow case in this chapter and read in the context of such suggestions.

In the wake of successful prosecution by federal officials in a case that received much publicity and attention from the public, the Executive Branch, and Congress, and FDA official circulated the following letter and attachments. These will certainly be influential with inspectors, although some of the positions taken may see argument in the future (p. 354 following).

Following study of this chapter, it might be helpful for staff review, to discuss specific guides provided by the FDA to their field staff and others, that are pertinent as Regulatory Action Guidance.

Sec. 300.100 Inspection of Manufacturers of Device Components (CPG 7124.15)

BACKGROUND:

* Section 510(h) of the Federal Food, Drug, and Cosmetic Act declares that all registered firms are subject to inspection pursuant to Section 704.

Some manufacturers have been confused by 21 CFR 807.65, believing that exemption from registration also exempts them from inspection. This is not true. As defined under Section 201(h) of the Act, devices include components of devices, making manufacturers of device components subject to the provisions of section 704. Title 21 CFR 807.65(a) exempts manufacturers of medical device components from the registration and listing provisions of section 510 of the Act, if those components are the only items the manufacturer produces which have health care applications and they are sold only to other manufacturers. The exemption does not apply to manufacturers of components described in 21 CFR 807.20(a)(5) unless they are marketed only to registered device establishments for further processing. The exemption applies only to registration and listing. *

POLICY:

* Exemption from registration under 21 CFR 807 does not exempt the manufacturer of device components from inspection under section 704 of the act. *

* All manufacturers of device components are subject to inspection under section 704 of the Act. *

* Material between asterisks is new or revised *

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SUB CHAPTER 130 INSPECTIONS

Sec. 130.100 Inspectional Authority; Refusal to Permit Inspection (CPG 7151.01)

BACKGROUND:

The authority for duly appointed officers or employees of the Food and Drug Administration to enter and inspect establishments under the jurisdiction of the Federal Food, Drug, and Cosmetic Act is in Section 704 of the Act (21 U.S.C. 374).

Questions concerning the right to inspect such establishments have often been raised and litigated. The courts have upheld the legality of an FDA inspection if it is conducted at a reasonable time, within reasonable limits and in a reasonable manner *. Consent is not the basis upon which a Food and Drug inspection is conducted, and permission or authorization to inspect is not required from the firm to be inspected.

The Federal Food, Drug, and Cosmetic Act provides criminal penalties for refusal to permit a lawful inspection.

POLICY:

The legality of an FDA inspection, conducted at a reasonable time, and within reasonable limits, and in a reasonable manner, depends not on consent but on the validity of statutory authority. An inspection warrant is not a prerequisite to lawful inspection pursuant to such authority. Refusal to permit inspection, upon presentation of official notice by appropriately identified Food and Drug Administration officers or employees pursuant to 21 U.S.C. 374, exposes any person responsible for such refusal to criminal penalties under 21 U.S.C. 331(f) and 333.

* *United States v. Biswell*, 92 S. Ct. 1593 (1972)

United States v. Del Campo Baking Mfg. Company, 345 F. Supp. 1371 (D., Del., 1972)

United States v. Business Builders, Inc., 353 F. Supp. 1333 (N.D. Okla., 1973)

Issued: 10/1/80

Sec. 130.200 Inspection of Firms when Legal Action Is Pending (CPG 7153.01)

BACKGROUND:

Inquiries from the field have indicated there is some confusion on whether or not to reinspect a firm while legal action is pending against that firm.

POLICY:

Reinspection of a firm should be based upon public health considerations. FDA has an obligation to determine compliance with the law even if a case is pending, and if on reinspection further violations are found, to take additional steps as necessary to bring about correction.

It must be clearly understood that cessation of a violation is not grounds for dismissal of a case. Prosecution actions particularly are based on violations that have already occurred, and nothing that takes place after the violation changes that fact.

Where a court requests, reinspection is also appropriate. A district should always be in a position to furnish the court with current information covering the defendant's operations. This does not mean, however, that FDA should perform an inspection of each firm just prior to arraignment or trial. As already indicated, unless a court requests an inspection, reinspection at that time is based upon public health considerations in light of priorities and available manpower.

Issued: 12/3/73

Revised: 10/1/80, 8/31/89

Sec. 130.300 * FDA Access to Results of Quality Assurance
Program Audits and Inspections * (CPG 7151.02)

BACKGROUND:

* Within all FDA regulated industries, some firms establish quality assurance units (QAU) to perform functions independently from the manufacturing or quality control organization. The QAU may periodically audit and critically review processes and procedures (for example, data collection, manufacturing practices, and quality control processes) to determine whether established protocols and procedures have been followed.

In the preambles to the final regulations on Good Manufacturing Practice for Medical Devices (43 FR 31508; July 21, 1978) (21 CFR 820) and on Good Laboratory Practice for Nonclinical Laboratory Studies (43 FR 59986; December 22, 1978) (21 CFR 58), FDA announced its policy not to review or copy a firm's records and reports that result from audits of a quality assurance program when such audits are conducted according to a firm's written quality assurance program at any regulated entity. The intent of the policy is to encourage firms to conduct quality assurance program audits and inspections that are candid and meaningful. *

POLICY:

* During routine inspections and investigations conducted at any regulated entity that has a written quality assurance program, FDA will not review or copy reports and records that result from audits and inspections of the written quality assurance program, including audits conducted under 21 CFR 820.20(b) and written status reports required by 21 CFR 58.35(b)(4). *

FDA may seek written certification that such audits and inspections have been implemented, performed, and documented and that any required corrective action has been taken. District personnel should consult with the appropriate headquarters office prior to seeking written certification.

* FDA will continue to review and copy records and reports of such audits and inspections:

1. In "directed" or "for-cause" inspection and investigations of a sponsor or monitor of a clinical investigation;
2. In litigation (for example, and not limited to: grand jury subpoenas, discovery, or other agency or Department of Justice law enforcement activity (including administrative regulatory actions));
3. During inspections made by inspection warrant where access to records is authorized by statute; and
4. When executing any judicial search warrant.

FDA will continue to have access to, review, and copy records and reports required by regulation, relating to quality control investigations of product failures and manufacturing errors. *

* Material between asterisks is new or revised. *

Issued: 03/01/83
Revised: 03/16/89
Revised: 06/03/89
Revised: 01/03/96

Sec. 130.400 Use of Microfiche and/or Microfilm for Method of Records Retention (CPG 7150.13)

BACKGROUND:

The agency has received many questions concerning the use of microfiche and/or microfilm systems in lieu of the retention of original records. This Compliance Policy Guide is based on a May 11, 1979 response to a request for an Advisory Opinion on this subject. (Docket Number 77A-0270).

POLICY:

The Food and Drug Administration has ** published several regulations that permit the maintenance of certain recordkeeping systems in lieu of the retention of original records: good manufacturing practices for medical devices (43 FR 31508, July 21, 1978); good manufacturing practices for human and veterinary drugs (43 FR 45014, September 29, 1978); nonclinical laboratory studies (43 FR 59986, December 22, 1978). These regulations include the use of microfiche and/or microfilm. We therefore conclude that the utilization of a microfiche and/or microfilm reduction system in lieu of the retention of original pre-clinical, clinical, and related drug and medical device research records, and drug and medical device quality control and manufacturing records, is acceptable.

The preambles to these regulations, and the regulations, discuss the conditions applicable to the maintenance of reduction systems. These include the following:

1. All records must be readily available for review and copying by FDA investigators at any reasonable time.
2. All necessary equipment must be provided to facilitate viewing and copying of the records.

Sec. 150.100 Requests for Portions of Intermediate or End Products Resulting from FDA Sample Analysis (CPG 7150.18)

BACKGROUND:

FDA occasionally receives requests for microbiological cultures isolated from samples analyzed by FDA. Requests for other entities isolated, extracted, or produced by sample analysis, i.e., chemical isolates, extracts, filth debris, etc., may also be received, especially regarding consumer complaint samples.

The Federal Food, Drug, and Cosmetic Act, makes no provision for FDA to provide to requesters portions of end or intermediate products resulting from FDA sample analysis.

Section 702(b) of the act provides that, upon request, a part of an official sample of a food, drug, or cosmetic will be provided for examination or analysis to any person named on the label, the owner of the sampled product, or his attorney or agent. This section of the act applies to portions of the sampled commodity. It *does not* apply to intermediate or end products resulting from sample analysis. Portions of intermediate or end products resulting from FDA sample analyses will not be routinely provided to requesters from outside the agency, including consumers from whom samples have been collected as part of the complaint investigation.

Exceptions to this policy may be considered when the agency determines that providing portions of intermediate or end products to the requester would help resolve a serious public health matter or would benefit the public wellbeing. When a request appears to warrant such consideration, the request should be referred to the Office of Compliance within the appropriate center for review.

Issued: 3/23/88

Analytical Methodology Used by FDA—Drugs (CPG 7152.01)

BACKGROUND:

There have been continuing problems concerning the appropriate analytical methodology used by FDA laboratories in support of regulatory actions. In several cases regulatory actions have been disapproved and much analyst time wasted because the analyst did not adhere to the appropriate analytical method. Where regulatory actions are predicated upon analytical findings the appropriate methods are generally those stated in the USP/NF, an NDA, or a firm's Standard Operating Procedure, as applicable.

POLICY:

Where FDA sample analysis is a basis for regulatory action only the following procedures are considered appropriate, unless specific instructions to the contrary are given by Center for * Drug Evaluation and Research.*

1. For official drugs (USP/NF) the official compendial analytical methods are to be used, unless the FDA has promulgated regulations under Section 501(b) (or, for antibiotics, Section 507) of the Act prescribing appropriate tests or assay methods, in which case the regulations are to be followed.
2. A non-official drug which is the subject of a new drug application is to be analyzed by the method in the NDA or ANDA.
3. A non-official drug which is not a new drug is to be analyzed by the method used by the manufacturer as part of its standard operating procedures. If the FDA analyst has concern over the validity of the unofficial method, those concerns should be documented.
4. When analyzing a product by any of the above methods, the method must be strictly followed.

5. When a drug is not covered by the above situations, the analyst may select an appropriate method with which to analyze the product. In selecting the method first consideration should be given to any existing AOAC method because AOAC methods have withstood the rigors of collaborative study. Any method selected must have been properly validated. If not previously validated it must be validated when it is used. Validation data must be submitted with worksheets when regulatory action is recommended.
6. When the compendial, NDA, or firm's method is not satisfactory (e.g., due to an interfering substance, non-reproducible method, (etc.)), then this should be reported to the Division of Manufacturing and Product Quality (HFD-320) for further followup and guidance.

For surveillance samples such as those collected during a multiple drug survey, the laboratory may substitute a validated non-official method for the original analysis. However, any out-of-limit results must be confirmed by check analysis using the official or other appropriate method.

* Material between asterisks is new or revised *

Issued: 7/1/81

Revised: 9/1/86, 3/95

APPENDIX: A JUDICIAL INTERPRETATION OF INSPECTION REQUIREMENTS



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

May 14, 1993

Dear Colleague:

Judge Wolin's interpretations of Good Manufacturing Practice (GMP) issues contained in the court's ruling on 2/4/93 in USA vs. Barr Laboratories is being forwarded for your information. This summary has been sent to Food and Drug Administration field offices and to the inspection cadres throughout the field for their use during drug GMP and pre-approval inspections. Therefore, we felt it was important information to share with you with regard to future GMP and pre-approval inspections. You may wish to share this document with others in your organization as well.

We will continue to provide information to you that we feel may be useful. Please let us hear from you if there is a particular service or information you would like from the Food and Drug Administration. I can be reached at 301/443-6776 or fax 301/443-5153.

Sincerely yours,

Mary Ann Danello, Ph.D.
Director, Office of Small
Business, Scientific and
Trade Affairs

Enclosure

JUDGE WOLIN'S INTERPRETATIONS
OF GMP ISSUES
CONTAINED IN THE COURT'S RULING
IN USA Vs BARR LABORATORIES
2-4-93

1. USP STANDARDS

The court ruled that USP's established standards are absolute and that firms cannot stretch the USP standards. These standards provide established criteria upon which firms release their product.

2. FAILURE (OUT-OF-SPECIFICATION) LABORATORY RESULTS

Judge Wolin preferred to use the term "out-of-specification" (OOS) laboratory result rather than the term "product failure" which is more common to FDA's investigators. He ruled that an OOS result identified as a laboratory error by a failure investigation or an outlier test¹, or overcome by retesting² is not a product failure. OOS results fall into three categories:

- laboratory error
- non-process related or operator error
- process related or manufacturing process error

A. LABORATORY ERRORS

Laboratory errors occur when analysts make mistakes in following the method of analysis, uses incorrect standards, and/or simply miscalculates the data.

Judge Wolin provided specific guidance about the matter of determining when an error can be designated a laboratory error. Laboratory errors must be determined through a failure investigation to identify the cause of the OOS. Once the nature of the OOS result has been identified, it can be classified into one of the three categories above. He states that the inquiry may vary with the object under investigation.

¹ The court provided explicit limitations on the use of outlier tests and these are discussed in a later segment of this document.

² The court ruled on the use of retesting which is covered in a later segment of this document.

B. LABORATORY INVESTIGATIONS

The court said that the exact cause of analyst error or mistake can be difficult to pin down and that it is unrealistic to expect that analyst error will always be determined and documented, and he ruled that the "laboratory investigation consists of more than a retest". The inability to identify an error's cause with confidence affects retesting procedures, not the investigation inquiry required for the initial OOS result.

The analyst should follow a written procedure, checking off each step as it is completed during the analytical procedure. Laboratory test data must be recorded in notebooks; use of scrap paper and loose paper is to be avoided. These measures enhance the investigation process.

The court specifically identified procedures that must be followed when single and multiple OOS results are investigated.

For the single OOS result, the investigation must include the following steps and these inquiries must be conducted before there is a retest of the sample:

- the analyst conducting the test must report the OOS result to the supervisor
- the analyst and the supervisor must conduct an informal laboratory inspection which addresses the following areas:
 1. Discuss the testing procedure
 2. Discuss the calculation
 3. Examine the instruments
 4. Review the notebooks containing the OOS result

An alternative means to invalidate an initial OOS result provided the failure investigation proves inconclusive is the "outlier" test. The Court placed specific restrictions on the use of this test.

1. Firms cannot frequently reject results on this basis
2. The USP standards govern its use in specific cases
3. The test cannot be used for chemical testing results³

A full scale inquiry is required for multiple OOS results. This inquiry involves quality control and quality assurance personnel in addition to laboratory workers to identify exact process or non-process related errors.

The court ruled that when the laboratory investigation is inconclusive (reason for the error is not identified):

³ An initial content uniformity tests was OOS followed by a passing retest. The initial OOS result was claimed the result of analyst error based on a statistical evaluation of the data. The use of outlier test is inappropriate in this case.

1. Cannot conduct 2 retests and base release on average of three tests
2. Cannot use outlier test in chemical tests
3. Cannot use a resample to assume a sampling or preparation error
4. Will allow a retest of different tablets from the same sample when a retest is considered appropriate (see criteria elsewhere)

C. FORMAL INVESTIGATIONS

Judge Wolin ruled that formal investigations extending beyond the laboratory must follow the government's outline with particular attention to corrective action. He said the company must:

1. State the reason for the investigation
2. Provide summation of the process sequences that may have caused the problem
3. Outline corrective actions necessary to save the batch and prevent similar recurrence
4. List other batches and products possibly affected, the results of investigation of these batches and products, and any corrective action. Specifically:
 - examine other batches of product made by the troublemaking employee or machine
 - examine other products produced by the troublemaking process or operation
5. Preserve the comment and signature of all production and quality control personnel who conducted the investigation and approved any reprocessed material after additional testing

D. INVESTIGATION DOCUMENTATION

Analyst's mistakes, such as calculation errors, should be specified with particularity and supported by evidence. Investigations along with conclusions reached must be preserved with written documentation that enumerates each step of the review in the form of a "computer generated flow sheet". This writing should be preserved in an investigation or failure report and placed into a central file.

E. INVESTIGATION TIMEFRAMES

All failure investigations must be performed within 30 business days of the problem's occurrence and recorded and written into a "failure or investigation report".

F. PRODUCT FAILURES

An OOS laboratory result can be overcome (disregarded) when laboratory error has been documented. However, non-process and process related errors resulting from operators making mistakes, equipment (other than laboratory equipment) malfunctions, or a manufacturing process that is fundamentally deficient, such as an improper mixing time, represent product failures.

3. RETESTING

Several opinions about retesting were issued in this decision. The number of retests performed before a firm concludes that an unexplained OOS result is invalid or that a product is unacceptable is a matter of scientific judgment. The goal of retesting is to isolate OOS results but retesting cannot continue ad infinitum.

In the case of non-process and process-related errors, retesting is suspect. Because the initial tests are genuine, in these circumstances, additional testing alone cannot infuse the product with quality. The court acknowledges that some retesting may precede a finding of non-process or process-based errors. Once this determination is made, however, additional retesting for purposes of testing a product into compliance is not acceptable.

For example, in the case of content uniformity testing designed to detect variability in the blend or tablets, failing and nonfailing results are not inherently inconsistent and passing results on limited retesting do not rule out the possibility that the batch is not uniform. As part of the investigation, firms should consider the record of previous batches, since similar or related failures on different batches would be a cause of concern.

A very important ruling in this decision sets forth a procedure to govern the retesting program. The judge ruled that a firm should have a predetermined testing procedure and it should consider a point at which testing ends and the product is evaluated. If results are not satisfactory, the product is rejected.

Additionally, the company should consider all retest results in the context of the overall record of the product. This includes the history of the product⁴, type of test performed, and in-process test results. Failing assay results cannot be disregarded simply on the basis of acceptable content uniformity results being satisfactory.

Retesting following an OOS result is ruled appropriate only after the failure investigation is underway and the failure investigation determines in part whether retesting is appropriate. It is appropriate when analyst error is documented or the review of analyst's work is "inconclusive", but it is not appropriate for non-process or process-related errors.

The court ruled that retesting:

- must be done on the same, not a different sample
- may be done on a second aliquot from the same portion of the sample that was the source of the first aliquot
- may be done on a portion of the same larger sample previously collected for laboratory purposes

⁴ The court ordered a recall of one batch of product on the basis of an initial content uniformity failure and no basis to invalidate the test result and on a history of content uniformity problems with the product.

4. RESAMPLING

Firms cannot rely on resampling⁵ to release a product that has failed testing and retesting unless resampling is in accord with the USP standards (content uniformity and dissolution), or unless the failure investigation discloses evidence that the original sample is not representative or was improperly prepared.

5. AVERAGING RESULTS OF ANALYSIS

Averaging can be a rational and valid approach, but as a general rule this practice should be avoided⁶ because averages hide the variability among individual test results. This phenomenon is particularly troubling if testing generates both OOS and passing individual results which when averaged are within specification. Here, relying on the average figure without examining and explaining the individual OOS results is highly misleading and unacceptable.

Content uniformity results never should be averaged to obtain a passing value for content uniformity.

In the case of microbiological assays an average is preferred by the USP. Also, the Judge ruled that it is good practice to include OOS results in the average, unless an outlier test (microbiological assays) suggests the OOS is an anomaly.

6. REMIXING

The need to remix often is clear indication that the process is invalid and casts doubt on those batches passed through testing without incident.

Remixing is reworking permitted under the GMP regulations. Occasional remixing is acceptable, but frequent or wholesale remixing is unacceptable.

7. PRODUCT RELEASE

Scientific judgment can play a role when firms decide to release a batch to the public and the court said it cannot articulate specific procedures for release decision making. However, Judge Wolin said that the USP standards upon which firms release their products are absolute and cannot be stretched. For example, a limit of 90 to 110 percent of declared active ingredient, and test results of 89, 90, 91, or two 89's and two 92's all should be followed by more testing.

It is clear that the release evaluation depends in part on the background of the batch and product.

⁵ The court ordered the recall of one batch of product after having concluded that a successful resample result alone cannot invalidate an initial OOS result.

⁶ The court ruled that the firm must recall a batch that was released for content uniformity on the basis of averaged test results.

Secondary factors that affect the actual finished product results as well as their reliability are:

- Physical properties
- Blend evaluations
- Time of mix
- Tablet weight, thickness, and friability

Judge Wolin ruled that context and history⁷ inform many final conclusions and that one must consider past problems with the product and batch and evaluate all the data relative to the product and batch.

8. BLEND TESTING

Blend testing is necessary to increase the likelihood of detecting inferior batches. Blend content uniformity testing cannot be waived in favor of total reliance on finished product testing because finished product testing is limited.

The court ruled that sample size influences ultimate blend test results and that the sample size should resemble the dosage size. Any other practice would blur differences in portions of the blend and defeat the object of the test. The appropriate sample size for blend content uniformity in both validation and ordinary production batches is three times the active ingredient dosage size.

Multiple individual samples taken from different areas cannot be composited. However, when variation testing is not the object of assay testing, compositing is permitted.

Firms must demonstrate through validation that their sampling technique is representative of all portions and concentrations of the blend. This means that the samples must be taken from places that might be problems, weak or hot spots in the blend.

In this case, the firm maintained that samples could be collected from the drums containing the finished blend. The court ruled that the firm must demonstrate that sampling from drums rather than the mixer is representative. He also ruled that the firm cannot composite blend samples and that they must take smaller blend content uniformity samples.

9. VALIDATION CRITERIA

A. RETROSPECTIVE VALIDATION

The court ruled that batches meeting the following criteria must be included in retrospective validation studies:

⁷ On the basis of an initial content uniformity failure and no basis to invalidate the test result and on a history of content uniformity problems with the product, the court ordered the batch recalled.

1. All batches made in the specified time period chosen for study must be included unless the batch was made from a non-process related error
2. Only batches made in accord with the process being evaluated can be included

Only test results determined through an appropriate failure investigation and found to be caused by analyst or operator error can be excluded from the study. Test results that are explained but merely called into question by successful retesting must be included in the study. The exclusion of batches and test results must be documented through failure investigation.

The number of retrospective batches chosen for the study must be greater than the number used for prospective validation. Although the court set no exact number of batches to be chosen, guidelines have been established as follows:

- Five batches is unacceptable and also 6 or more may not be acceptable
- Because a 10% batch failure is unacceptable, if one batch fails, more than 10 batches are needed for the retrospective study
- Experts accept 20 to 30 batches

B. CONCURRENT AND PROSPECTIVE VALIDATION

Concurrent and prospective validation requires at least three consecutive batch runs of the process.

Mixing time studies should be included in a prospective validation program and follow any problems that surface in retrospective validation batches.

Particle size distribution specifications are widely accepted industry practice and should be included in validation studies.

10. SIGNIFICANCE OF APPLICATION APPROVALS

The court ruled that a firm cannot rely on the claim that the FDA previously approved their procedures contained in an approved application. This approval cannot be used as a defense and cannot be used to shield a process that produces failures.

11. METHODS VALIDATION

Methods can be validated in a number of ways. Methods appearing in the USP are considered validated and they are considered validated if part of an approved ANDA. Also, a company can conduct a validation study on their method. System suitability data alone is insufficient for method validation.

12. CLEANING VALIDATION

The court ruled that a firm cannot wait for contamination and other problems to reveal inadequate cleaning procedures. In order for the cleaning rules to be effective, the specific

methods chosen must be shown to be effective.

The court ruled that a milling machine is a major piece of equipment and must be included in the cleaning validation program.

Firms must identify the cleaning agents used in its cleaning process. When these agents are known to cause residue, the company must check for the residue.

Provided the firm has described its cleaning methods and materials in sufficient detail

AND

Unless the cleaning material is known to cause a residue

THEN

one run through of the cleaning procedure, in the absence of problems, is not insufficient for validation.

EFFECTIVELY MANAGING OSHA INSPECTIONS

Introduction

How an employer prepares for and manages an inspection conducted by the Occupational Safety and Health Administration ("OSHA") can go far to minimizing the severity of any citation that may issue in connection with that inspection. This article will discuss the basic steps in an OSHA inspection and some of the critical points that an employer should keep in mind when confronted with such an Agency investigation.

The Field Inspections Reference Manual ("FIRM"), which is OSHA's guidance to its compliance safety and health officers ("CSHOs"), describes four categories of inspections under the Occupational Safety and Health Act of 1970, 29 U.S.C. §651 et seq. ("OSH Act"). These are unprogrammed inspections, unprogrammed related inspections, programmed inspections and programmed related inspections (FIRM, Chap. II, §B). An unprogrammed inspection is the type of inspection most often experienced by employers. It includes complaint, fatality/catastrophe, referral, imminent danger, follow-up and monitoring inspections. A programmed inspection is one that has been scheduled based upon objective or neutral selection criteria where the work sites are selected according to national scheduling plans for safety and for health or pursuant to a special emphasis program such as the PetroSEP, involving the petrochemical industry, or the Ergonomics Special Emphasis Program in Regions I and III. The "related"

inspections are inspections of employers on multi-employer work sites whose activities were not included in the underlying unprogrammed or programmed inspection.

OSHA inspections generally consist of certain fixed stages and involve recurrent issues. Being aware of what to expect from the Agency at each of these stages in the inspection helps the employer to respond properly and, where appropriate, effectively to assert its rights when OSHA overreaches its authority.

The Complaint and/or Warrant

When OSHA arrives at the work site, employers should inquire of the CSHO as to the type of inspection. If the inspection has been catalyzed by a complaint, the employer should ask to review a copy of the complaint. In a federal OSHA jurisdiction and most state plan states (California being the exception), the employer will be given, or at minimum shown, a copy of the complaint with the name of the complaining individual redacted. Employers should carefully scrutinize the complaint. First, this will give the employer an idea of the issue(s) in which OSHA is interested. Second, in those jurisdictions that take a narrower view of the probable cause element of an OSH Act warrant, the subject matter of the complaint may provide the basis for a challenge to the scope of a warrant or a subpoena for documents.

Provided by Vedder, Price, Kaufman and Kammholz.

Although the OSH Act does not mention the employer's right to demand a warrant for non-consensual inspections, that right was secured for employers in *Marshall v. Barlow's Inc.*, 436 U.S. 307 (1978). Whether to ask the CSHO for a warrant before allowing an inspection is in large part a function of both the corporate culture and the court of appeals jurisdiction in which the inspected work site is located. Currently, there is a split among the circuits that have addressed themselves to the issue. For example, the Fourth, Seventh, Eighth and Ninth Circuits have concluded that even a specific complaint, referencing a particular department or operation, is sufficient to justify a warrant for a "wall-to-wall" inspection. By contrast, the Third and Eleventh Circuits have taken a more restrictive view. As for the "corporate culture" element, most employers do not choose to make OSHA get a warrant, concluding that it is too adversarial an approach. Of course, the issue may not be up to the employer if OSHA shows up with an anticipatory warrant. In such cases, OSHA, usually based on past history with the employer, believes that the employer may turn the CSHO away without a warrant and so the Agency seeks an *ex parte* warrant before showing up at the employer in the first instance.

Whether or not the employer makes OSHA get a warrant or OSHA shows up with an anticipatory warrant, the employer should carefully scrutinize any warrant presented to determine its temporal as well as its geographical scope. In some instances, for example, the warrant is limited in terms of time or plant location. Clearly, if such a limitation is set forth in the warrant, OSHA should not be permitted to go beyond those limitations in conducting the inspection.

Asking the CSHO to Wait

It is best for the employer to have preselected an employer representative to handle the inspection and interface with the CSHO. This person should have received prior training in the rights and responsibilities of employers during OSHA inspections so as to

avoid providing more data to the Agency than may be legally required and to ensure that the CSHO stays within appropriate investigative limits. If this employer representative is not immediately available but can be on site within a limited amount of time, such as two or three hours, the employer should courteously request that the CSHO wait until the arrival of this company point person. Although the CSHO may not be happy waiting, he or she knows that it will take far longer than an hour or two to obtain a warrant entitling the Agency to mandatory access.

The Opening Conference

The OSHA inspection begins with an "opening conference". The employer should utilize the opening conference to get an idea from the CSHO as to the operations in which the Agency is interested and the scope of the inspection in terms of length and plant operations. If it appears that the inspection will be prolonged and comprehensive, the employer should try to work out with the CSHO "ground rules" for how the inspection will be conducted.

Document Requests

Generally, employers should insist on written document requests from OSHA in order to allow for analysis of possible objections, to assist in keeping track of produced documents and to build in sufficient time to ensure proper compliance. Exceptions to this general principle are documents that OSHA requires be kept and made available for inspection in the normal course, such as OSHA 200 Logs and Form 101s and commonly required written programs, *e.g.*, Hazard Communication, Lockout/Tagout, Hearing Conservation, Respiratory Protection, Bloodborne Pathogens, Confined Space, Emergency Action, HAZWOPER and PSM. Employers must also ensure compliance by OSHA with the Medical Access Order requirements for review of personally identifiable employee medical records.

THE WALK-AROUND

An employer representative should *always* accompany the CSHO when he or she conducts the walk-around inspection. The CSHO will also probably ask for an hourly employee representative to participate in the walk-around. While on the walk-around, the employer representative should not get into an extended dialogue with the CSHO or try to defend when the CSHO identifies a possible violation. First, this could lead to damaging admissions. Second, the employer representative may unknowingly undermine or dilute certain defenses available to the employer. Rather, the representative should merely answer specific questions such as how something works, what something is, whether it runs for three shifts, etc.

Employee Interviews

The employer has the right to be present at interviews by OSHA of management personnel. These interviews by the CSHO should be scheduled and management witnesses should be properly prepared as they are with virtually all other government investigation interviews or depositions. Although the CSHO will often request to interview certain management staff members immediately, they are not entitled to such instant gratification or to disrupt your normal operations. Again, the employer representative should politely but firmly inform the CSHO that the individual he or she seeks to interview is not immediately available and then arrange a time and place for the interview. Whether an attorney should be present for the preparation and/or the interview is a function of the type of inspection and the potential for substantial liability. Clearly, if there is a fatality/catastrophe inspection which carries with it the potential for criminal and/or willful liability, an attorney should get involved immediately and be present for all management interviews. However, if the inspection is routine, attorney involvement in the interviews may not be required.

With respect to interviews of hourly employees, OSHA generally takes the position that it can and should interview these employees outside the presence of management. If the employer refuses OSHA that opportunity, the Agency will subpoena the home addresses and telephone numbers of employees and will pursue interviews off site. If OSHA identifies for scheduling purposes the hourly employees it seeks to interview, the employer has the right to speak with the employee first and inform the employee that he or she may request that a management representative be present if the hourly employee so chooses.

Sampling, Videos, Trade Secrets and Contractors Issues

Sampling of employees and the workplace environment along with photographing and videotaping are all inspection techniques used by OSHA and upheld by the courts. Although an employee can not be compelled to wear a sampling device and although an employer may tell the employee of his or her right to refuse to participate in sampling, it is generally advisable to respond to employee inquiries regarding the right to refuse rather than to initiate the advice in order to avoid the appearance that the employer is encouraging lack of cooperation by its employees.

The OSH Act provides for protection of trade secrets. However, this protection does not mean that the inspection of the proprietary equipment or operation will be forestalled; rather, it is the employer's responsibility to identify to the CSHO what is a trade secret; thereafter, the CSHO is obligated to ensure that the identified matter is treated in accordance with Agency guidelines providing for its protection.

Contract workers are an increasing source of OSHA concern and the Agency takes an expansive approach towards their coverage. Given this clear expression of OSHA interest and the attendant liability employers may face for contractors, it is

essential that the employer keep abreast of the legal issues with respect to contractors as they develop.

The Closing Conference

After the inspection is completed but before the citation issues, the CSHO will hold a closing conference to review the inspection findings in a general fashion. Generally, the CSHO will not discuss penalties and will not specifically reference the classifications of the alleged violations. Employers should primarily listen and not try to defend against the identified violations. It is usually too late at this point to change the CSHO's mind unless there is a very clear and apparent mistake of fact. For example, if the CSHO states that the employer is to be cited for not having a written Bloodborne Pathogens Program and the employer in fact has one that inadvertently was not shown to the CSHO during the inspection, then the employer should point that out during the closing conference. However, attempts by the employer to defend against the violations referred to by the CSHO in the closing conference could result in adverse admissions or other statements that could undermine available defenses. For the same reasons, it is advisable not to respond to the CSHO's inquiries as to how long the employer thinks it will need to abate an identified violation. The CSHO will take a response as an admission that abatement is required, although a defense may be applicable. Additionally, if the employer has not realistically estimated the time needed for abatement, it may be necessary to recant after the citation is issued and OSHA has incorporated into the citation the employer's own abatement estimate.

* * * * *

Given the greatly increased liability for employers under the OSH Act and under state criminal statutes for workplace illness and injury, it is crucial for employers to properly prepare for and effectively

manage OSHA inspections. Employers should be aware of evolving and expanding theories of liability. They should also be careful to assert their rights during the inspection such as preparing witnesses for interviews, objecting to overbroad document requests and being very careful not to alert OSHA to documents and witnesses about which the CSHO may not be otherwise aware.

FDA Pre-Approval Inspections/ Investigations; The Road from SUPAC to the Food and Drug Modernization Act

Largely as a result of the inclusion of falsified data in some ANDA submissions, the FDA introduced the Pre-Approval Inspections/Investigations Compliance Program (7346.832) in 1990. This involved the FDA district offices directly in the drug-approval process. The role of the district is to “assure CGMP compliance, verify the authenticity and accuracy of the data contained in the applications, and report any other data which may impact on the firm’s ability to manufacture the product in compliance with the GMP’s.”

A Pre-Approval Inspection (PAI) will be requested by a reviewing chemist for any of the following:

- The product has a narrow therapeutic range—a list of such products is included in the Guide

- New chemical entities

- Generic versions of the 200 most prescribed drugs

- When the GMP status for the dosage-form manufacturer is unacceptable or the facility has not been inspected for 2 or more years

- The initial application from a company

- The first generic application of a branded product

- The reviewing chemist identifies potential deviations or discrepancies in the submission

Bulk pharmaceutical chemical manufacturers and support operations (contract operations for processing, labeling, packaging, or testing) where there has been no recent GMP inspection

Supplements involving new facilities or major alterations to existing facilities—dosage form, bulk drug, or control laboratory.

District offices may also initiate their own inspections if they consider this to be necessary.

The PAI emphasis includes:

Facility CGMP compliance and the capability to produce the product. This applies to the producers of dosage forms and drug substances and may be extended to the producers of novel excipients. The PAI is sometimes used as another opportunity to evaluate a manufacturer with respect to general GMP compliance. Since facilities are routinely inspected for GMP compliance, this review should be unnecessary unless previous inspections had identified areas for improvement or the technology is new to the facility. With the limited availability of FDA resources, this would seem an activity that could be curtailed.

A significant reason for a nonapprovable recommendation has been the inability of the company to manufacture the product on a commercial scale. The scale-up work and supporting stability batches were produced on pilot-scale equipment and the full-scale facility/equipment was not available. In such circumstances companies can ask for a delay in the inspection.

Process validation. The FDA agreed that the validation data need not be available at the time of the PAI. However, the approved protocols should be in place and the validation must be completed before product is distributed. This is a very practical approach since validation involves a minimum of three commercial-scale batches, which can be very costly. By performing validation studies closer to the anticipated approval date, the batches can usually be made commercially available, thereby recovering some of the costs. The FDA inspectors may wish to evaluate the completed validation package, but this can occur after approval and commercialization of the product. In the event that the data are found to be inadequate, the product may have to be recalled or further production not allowed until the validation is repeated.

The situation is different for foreign operations. Because of the cost and resource implications associated with foreign inspections, it is usually impracticable to arrange a follow-up inspection to review validation data. Consequently, the validations are expected to be completed at the time of the PAI. This does, of course, add extra cost to the manufacturer, since in most instances these batches will have expired or be close to expiration by the time FDA approval is received. Hopefully, if the approval cycle time is reduced considerably, this may become less of a problem.

For products involving aseptic processing or sterilization, reviewing chemists normally require that some validation data be included in the submission to demonstrate that these specific processes are qualified.

The Guide also indicates that the validation requirements for BPCs need not be so extensive and the main objective is to ascertain that the production processes are adequately defined and perform consistently. Identification of the failure (reject, rework, production deviation) of a significant number of batches is considered evidence of nonconsistency.

Data accuracy and completeness. The FDA investigator will review raw data and compare this with the NDA/ANDA submission. The intent is twofold. First is to ensure that no data has been excluded. All data should be included in the submission with appropriate comments where the data is considered to be irrelevant. The second intent is to determine whether any of the submitted data appears to be fraudulent. The FDA places a heavy emphasis on this issue, and unfortunately there have been examples of fraudulent data submission.

Biobatch. The field investigator is expected to specifically examine the GMP compliance of key batches—those used in pivotal clinical studies, for bioavailability/bioequivalence, and for stability.

Laboratory methodology. The FDA field analytical laboratories will validate the analytical methods included in the submission. The Guide includes comprehensive details of samples required for validation and also for other evaluations (forensic and biotest).

The PAI provided the FDA district offices with considerably more “muscle” than ever before. Previously, any CGMP violations, or interpretive violations, resulted in the issuance of a FDA 483 citation. The company involved usually responded giving details of the remedial actions being taken. Unless the violations were considered significant, requiring further action, the commercial activities of the company were not adversely impacted. For most companies the corrective actions were initiated expeditiously. The PAI provided the FDA districts with the opportunity to recommend nonapproval of an NDA/ANDA/Supplement until the appropriate corrective actions had been implemented and confirmed by reinspection. The potential loss of profit resulting from delays in approval was enough to ensure that company top management supported the corrective actions and provided any needed resources. On the negative side, an interpretive violation could also delay approval. In recent years the FDA has reduced its level of control from Washington and has allowed considerable local freedom. This has resulted in some cases of unnecessarily aggressive interpretation of the CGMPs by some investigators being used to delay approvals.

PAIs can be scheduled at any time after the receipt and initial review of the submission for completeness. Preparation for a PAI should be a team effort frequently led by QA. Some key steps in the preparation include:

Confirmation of GMP compliance at all sites. This could involve a review of all recent quality inspections by any source with confirmation that any required remedial actions had been completed. This should be supplemented by a further GMP audit of each facility.

Collation of data. Raw data and supporting documentation should be collected so that they are readily available for review by the investigator. This also provides a useful opportunity to perform an internal reassessment on the data to ensure that any deviations were adequately evaluated. Special emphasis should be placed on data relating to the biobatches and stability batches.

Review of the technology transfer data, from R&D to plant. This will include validation protocols (and possibly IQ and OQ data on equipment), operator and analyst training, analytical methods verification, and comparison of scale-up batch processing details with the biobatches.

Confirmation that the development report, which describes the history of the development of the product, is comprehensive and clear.

While the preparation for a PAI, as just outlined, is essential, this is really too late to rectify any serious issues or omissions. However, it does allow time to prepare an explanation and possibly to compile a protocol for any additional work that may be required. The most effective way to assure a PAI recommendation for approval is to perform the entire development process in compliance with requirements:

Train personnel in GMP, GLP or GCP as appropriate and ensure that they are fully aware of the importance of compliance—good science and regulatory impact.

Managers and supervisors to *constantly* monitor compliance and to initiate appropriate actions when deviations are observed. This continuous attention also enhances the awareness of the importance of compliance to personnel.

Document all deviations at the time they occur, with supporting evaluations.

Have a development and technology transfer process that clearly defines accountabilities and responsibilities.

Provide continuous audit of the process and data.

Since the introduction of the PAI, the level of recommendations for nonapproval has moved from approximately 60% in 1990 to 30% in 1994.

The most common causes for these recommendations to withhold approval were lack of plant capability to produce the product; general GMP deviations including lack of production batch records, incomplete failure investigations, incomplete cleaning validation, and stability program deficiencies; and laboratory

problems such as discarding of initial raw data after repeat testing, failure to calibrate laboratory equipment, and incomplete laboratory notebooks. Fraud was implicated in 2% of these cases.

Overall the PAI has had an impact in improving the level of GMP compliance. However, it has also increased product costs and delayed product introductions. At this time no other regulatory authority has introduced an equivalent program.

FDAM ACT AND MANUFACTURING CHANGES TO APPROVED DRUGS

The Food and Drug Administration Modernization Act was intended to be fully effective on November 26, 1999. Some small parts have been declared unconstitutional but they do not affect its impact on manufacturing and quality control. The latter, with a special note as to the manufacturing changes to approved drug applications, have undergone changes somewhat favorable to manufacturers, who in the past hewed closely to the statutory requirements in the FFDC Act and 221 EFR 314.70 of the regulations.

The “Modernization Act” does provide a relative approach concerning manufacturing changes unlikely to impact on quality versus those that do, and much remains for the regulators to determine as to their implementation.

Bearing in mind that the FDA, a so-called executive agency, itself answered the criticism of industry in that it often required, somewhat inflexibly, an investment of time and money in the costly submission of prior approval manufacturing supplements for minor changes. The FDA Scale-Up and Post Approval Changes (acronym SUPAC) process was their answer, and while the spirit of the response was good for manufacturers, industry has yet to discern the heavier changes in regulation they seek.

There have been a more substantial number of change-being-effected (CBE) supplements noticed to the FDA by inclusion in an annual report, but large-scale manufacturers are hesitant because distribution is at their own risk during the pendency of review of the supplement. In general, conservative CBE supplements are related to changes that seem to make more certain the anticipated detection and effect of the drug substance will be maintained. Less-conservative ones depend on changes that will be deemed inconsequential to maintenance of the anticipated effect of the drug substance. .21 CFR 314.70 (a), (b), (c), (d) are the regulatory guidelines for supplements that may or may not be made before FDA approval and form a reliable baseline for a determination by those who regulate and those regulated. Some changes may be for notation in the annual report .21 CFR 314.70 (d).

Therefore, when the FDA undertook the SUPAC approach to the process with the National Performance Review staff, it was made public that the FDA was proposing reforms that could save the drug and device industry a half billion dollars annually. FDA's Center for Drug Evaluation and Research was charged with the responsibility of developing a guidance document for drugs in tablet and capsule form (other than those for controlled release) to ease existing rules for manufacturing changes.

The SUPAC-IR Notice appeared in the Federal Register (60FR61.637 {1995}) "Immediate Release Solid Oral Dosage Forms; Scale Up and Post Approval Changes: Chemistry, Manufacturing and Controls; In Vitro Dissolution Testing; In Vitro Bioequivalence Documentation. One must, however, regard this as a preliminary to the implementation of FDA's authority, apparent or assumed, as FDAMA and its regulations become the statutory guides for the end of 1999. Whether written or unwritten, as an internal strategy, the use of Levels of Change by the FDA is probably here to stay because the FDA has used them informally before addressing them specifically in the published SUPAC-IR notice previously mentioned. Therefore, it remains important for the manufacturer's judgment to have the capability of documenting effectively the minor variations that can be checked by mantle of Level 1 Changes, which require that the supportive information simply be included in a subsequent annual report.

Bear in mind that the progenitor of the SUPAC-IR Notice was not merely the "reinventing government" push of the Administration. It was a product of a 4-year joint effort that our prior edition has considered for its inclusion of academic and industry groups. It was actually prepared by the SUPAC Expert Working Group of the Chemistry Manufacturing Controls Coordinating Committee of the FDA's CEDER, with contributions from the American Association of Pharmaceutical Sciences in conjunction with the United States Pharmacopeial Convention. It incorporated suggestions generated by research from many universities and colleges, among them the University of Maryland (Baltimore) and Michigan.

The FDA apparently believes that the SUPAC-IR guidelines fit comfortably within established regulatory mechanism. See, in part, in 314.70 (a) ". . . an applicant shall make a change provided for . . . in accordance with a guideline, notice or regulation published in the Federal Register that provides for a less burdensome notification of the change . . ."

Considering that the purpose of the enactment of the Food and Drug Administration Act of 1997 (FDAMA) was to improve regulatory efficiency of drugs, medical devices, and food, without undermining established discretionary authority of the FDA, it was destined to be a welcome law to some and disappointing to other regulatees. In fact, in another section we have outlined an area of challenge that has been visited by the Judiciary.

But as to the new section of the FFDC Act added, 506A, to which we direct ourselves here, the requirements for approval of manufacturing changes for drugs

and biologics have given optimism to global manufactures. The Level of Change has been statutorily visualized, with aid from new regulations, to be “major” or “other.” All “changes” are defined as those determined to have a substantial potential to adversely impact the identity, strength, quality, purity, or potency of the drug as those characteristics relate to the safety and effectiveness of the drug in terms of its approved labeling. Therefore “major” changes are statutorily defined at 21USC 506A[®] (see Appendix A hereto). Every established manufacturer with approximately educated and trained personnel can make such determination with reasonable accuracy.

But the Act holds promise: the SUPAC style handling of the “other” changes, the CBE supplement, seem to be simplified and time shortened, perhaps the site transfers for manufacturing and packaging and changes in equipment that are fairly common.

The FDA, it is emphasized, continues to have great force because it is the judge of what changes are “major” and which are “other”; which of course means a determination of time, expenditures, and special or usual personnel needs for the changes. Thus, the SUPAC-IR Notice and various regulations will play a part in the new statutes’ constructive effect on manufactures but it is that statute and its implementing regulations that will provide the seminal strain of law and policy.

An important role for the FDA, aside from its statutory change, will be how it uses three major areas of discretion set out in FDAMA. History bodes well. The FDA will not be a bully, it will be appreciative of the needs of manufacturers and other distributors while it exerts its own quality control mechanism in protection of consumers. Already several guidances issued by the FDA to implement key provisions of the FDAMA are available (800-899-0391). Internet access numbers are also available from the FDA.

SUGGESTED READINGS

1. Manufacturing Changes: “From SUPAC to FDAMA,” Pinco, Jiminez, Katdare, FDCMD Law Digest, Vol. 15, No. 3, 1998.
2. “FDAMA, Its Impact on Medical Devices,” Connolly, 15 FDCMOL Digest 60 (1998).
3. 15 FDCMDL Digest 64 (1998), Wu and Mazan.
4. “The Food Revisions of the Food and Drug Modernization Act”, Rodriguez, 15 FDCMDL Digest 15 (1998).
6. “FDA Compliance Program Guidance Manual (7346.832)—Pre-Approval Inspections/Investigations,” 1994.
7. R. M. Justice, J. O. Rodriguez, and W. J. Chiasson, Ten Steps to Assure a Successful Pre-NDA Approval Inspection, *J. Parenteral Sci. Technol.*, 47(92), 89, 1993.
8. M. Wells, Foreign FDA Pre-Approval Inspections: Requirements/Preparation. *J. Pharm. Sci. Technol.*, 48(6), 330, 1994.

9. "FDA Guide to the Inspections of Oral Solid Dosage Forms. Pre-/Post Approval Issues for Development and Validation," January 1994.
10. "FDA Guide to Inspection of Oral Solutions and Suspensions," August 1994.
11. "FDA Guide to Inspection of Dosage Form Drug Manufacturers—CGMPs," October 1993.
12. "FDA Guide to Inspection of Topical Drug Products," July 1994.
13. "FDA Guide to Inspections of Lyophilization of Parenterals," July 1993.

Following study of this chapter, it might be helpful for staff review, to discuss specific guides provided by the FDA to their field staff and others, that are pertinent as Regulatory Action Guidance.

COMPLIANCE POLICY GUIDES

SUB CHAPTER 440 NEW DRUGS

Sec. 440.100 Marketed New Drugs Without Approved NDAs or ANDAs (CPG 7132c.02)

BACKGROUND:

Prior policy under the DESI program had permitted a firm to market a new product upon the submission of a New Drug Application (NDA) or Abbreviated New Drug Application (ANDA) as long as the new product was identical to a prescription drug product that had been evaluated as "effective". The history and justification for this approach were described in a FEDERAL REGISTER notice published on June 20, 1975 (40 FR 26142, see paragraph I(D)(5) on pp. 26144-45). This policy was challenged and overturned in a lawsuit on July 29, 1975 (Hoffman-La Roche v. Weinberger, 425 F.Supp. 890 (D.D.C. 1975)). The Court held that if FDA had declared a prescription drug product to be a "new drug", the agency could not permit any identical, similar, or related product to be marketed without prior approval of an NDA or ANDA. The complete text of this decision was published in a FEDERAL REGISTER notice on September 22, 1975 (40 FR 43531). Subsequently, the Court granted certain exceptions to this ruling, but these exceptions are not applicable to DESI effective drugs. The amendment to the Court's order was published in the FEDERAL REGISTER on March 2, 1976 (41 FR 9001). It should be noted that all drugs in the DESI review are "new drugs" under the law.

As a result of this decision, the agency has reevaluated its policy, the resources available to process NDAs and ANDAs and to handle violations of the law, and the alternative policies which might be used to protect the public health and safety within the requirements of the Federal Food, Drug, and Cosmetic Act. The agency has decided to reaffirm that all products marketed as drugs under the DESI program are new drugs, and therefore, require an approved NDA or ANDA for marketing. In view of the reaffirmation of this policy, the agency must proceed to remove from the market all current DESI-effective prescription products that are not the subjects of approved NDA's or ANDA's, and to prevent in the future the marketing of such unapproved products.

The agency is aware that many firms are marketing products without approved new drug applications that are related to DESI effective prescription drugs. In order to achieve

uniform compliance with the Court Order, all violative products must be identified and removed from the market. With the resources presently available for attaining industry-wide compliance, this goal will take several years to achieve. Considering the magnitude of the problem, the limitation on FDA's resources, and the resulting long time period before compliance can be fully attained, the agency has developed a strategy to handle unapproved products on a priority basis. The priorities for enforcement action relate to a particular drug's effect on public health and safety, and are designed to have a maximum impact on violative products and to provide equitable treatment among competing firms. This strategy also integrates with ongoing compliance programs directed at DESI-effective prescription drugs, OTC Category II products, and post-1962 NDA prescription drugs, and anticipated compliance programs directed at DESI-Paragraph XIV prescription drugs (those requiring additional studies before a decision on effectiveness can be made), and pre-1962 new drugs which were not part of DESI.

POLICY:

Part A of this section outlines the sequence for relating drugs for which final determinations have been made regarding their new drug status and for which FEDERAL REGISTER notices have been published requiring ANDA or NDA approval for marketing them. All products within each category will be treated in the same fashion regardless of the size of the firm.

The Center for * Drug Evaluation and Research * will implement Part A of this policy by identifying those marketed drug products which are within the Part A categories named below. The District Offices will then initiate regulatory action against any violative products on the market in accordance with a Compliance Program regarding that specific category of drugs. This procedure will be repeated for each category until overall compliance is achieved. The * CDER * may from time to time add drugs to any category.

Part B of this section covers the regulation of those drugs for which final determinations regarding their regulatory or legal status have not been made.

1. DESI PRESCRIPTION DRUGS WHERE FINAL DETERMINATIONS ON EFFECTIVENESS HAVE BEEN MADE.

Category I—Ineffective Drugs

These are covered by an ongoing program (C. P. 7352.001) and will remain top priority.

Category II—Bio-Problem Drugs

This category consists of DESI-effective prescription drugs with known or potential bioavailability or bioequivalence problems.

Approximately 171 drug entities have been identified in this group. Regulatory action has already been initiated on those identical drugs identified in the DHHS Publication No. (FDA) 76-3009 (revised 6/76). The General Program (C.P. 7352.002) covering this category has issued and follow-up to this category is ongoing under Compliance Program Circular PC 7352.002D.

Category III—Top 200 Prescription Drugs

This category consists of the "Top 200" most widely prescribed drugs that have been DESI-rated as effective. This category does not include antibiotics, topical preparations, and those drugs listed in Categories I and II.

An initial survey indicated that there were approximately 25 drug entities in this category requiring attention. These “Top 200 Prescription Drugs” are identified in Program Circular 7352.002E. Regulatory Letters have issued from District offices to all known manufacturers of unapproved drugs subject to this category.

Category IV—Bio-Related Drugs

This category consists of all the prescription drugs related to those in Category II (i.e., drugs containing one or more of the listed ingredients). This category includes combinations, related chemical forms and related dosage forms, including controlled release. It excludes topical preparations. Controlled release preparations may warrant separate attention but this requires further evaluation. These “bio-related drugs” have been handled under Program Circular 7352.002C and regulatory letters have issued to all known manufacturers of unapproved drugs subject to this category.

Category V—Other Identical DESI-Effective Prescription Drugs

This category consists of those products that are identical to DESI-effective prescription drugs, excluding topical preparations, and are not covered by the preceding categories. These products will be handled under a Compliance Program similar to that used for Category II.

Category VI—Other Related DESI-Effective Prescription Drugs

This category consists of combinations and related chemical dosage forms including controlled release. It excludes topical preparations. Products subject to this category will be handled under a Compliance Program similar to that used for Category II.

Category VII—DESI Effective Prescription Topical Preparations Identical and Related

This category consists of all the topical preparations for the drugs covered in Categories I-VI. These products will be handled under a Compliance Program similar to that used for Category II.

B. DESI AND OTHER PRE-1962 PRESCRIPTION DRUGS WHERE FINAL DETERMINATIONS ON THEIR REGULATORY OR LEGAL STATUS HAVE NOT BEEN MADE.

These drugs are covered by the categories outlined below and may be worked into the regulatory scheme described under Part A above as final determinations are made regarding their effectiveness, new drug status, or grandfather status.

DESI “Paragraph XIV” Prescription Drugs.

This category consists of prescription drugs that are currently exempted from regulatory action under Judge Bryant’s Order. As final determinations are made regarding the effectiveness of these drugs, they will be handled under the appropriate Part A category on a continuing basis. That is, if a drug is downgraded to “ineffective” it will be handled under Category I, and if it is upgraded to “effective” it will be handled under one of the remaining Part A categories.

DESI “Less-Than-Effective” Prescription Drugs.

This category consists of prescription drugs for which final DESI determinations on effectiveness have not been made (e.g., possibly or probably effective drugs and those with current NOHs), other than those in the Paragraph XIV Category. As final determinations are made regarding the effectiveness of these drugs, they will be handled under the appropriate Part A category on a continuing basis.

Pre-1962 Prescription Drugs Covered by an NDA But Not Yet Reviewed by DESI.

A certain number of drugs covered by pre-1962 NDA's have not undergone a DESI review. Procedures are being implemented so that these drugs will be evaluated to determine their effectiveness. As final determinations are made on these drugs, they will be handled under the appropriate Part A category on a continuing basis.

Pre-1962 Prescription Drugs Not Covered by an NDA.

A certain number of drug products containing one or more active ingredients first introduced into the marketplace before 1962 are not covered by an NDA. These products are marketed based on their manufacturers' belief that such products are not subject to the new drug provisions of the act. Procedures will be implemented so that these products will be evaluated to determine whether the new drug provisions are applicable to them. If a final determination is made that a particular drug in this category requires an approved NDA or ANDA before marketing, the drug will be handled under the appropriate Part A category on a continuing basis.

POLICY GUIDELINE EXCEPTIONS:

While this policy guide represents a systematic approach to the implementation of the Court Order and the requirements of the new drug provisions of the act, it is not meant to preclude taking action against drugs outside of the established priorities under the following circumstances:

1. Including a new drug (505) charge (where appropriate) for a drug subject to this policy which become violative under another provision of the act.
2. Initiating regulatory action (as a new drug) against any drug subject to this policy should the agency receive significant new information which questions the safety or effectiveness of the drug.
3. Initiating regulatory action against any drug on the market without an approved new drug application if it is identical or related to a post-1962 NDA approved for safety and effectiveness or it contains a new chemical entity not previously marketed.
4. Initiating regulatory action against an unapproved prescription drug product first marketed after November 13, 1984, if the product differs from a product covered by Part B above in:
 - A. formulation (as described below);
 - B. dosage or strength;
 - C. dosage form;
 - D. route of administration;
 - E. indications for use; or
 - F. intended patient population.

A formulation will be considered different, if:

 - (1) the product contains a different active ingredient;
 - (2) the product contains a different quantity of an active ingredient;
 - (3) the product is a non-oral dosage form other than a topical preparation and it contains one or more different inactive ingredients, different amounts of inactive ingredients, or different proportions of inactive

ingredients to the extent that the names, amounts, or proportions of inactive ingredients are required by regulation to be disclosed in labeling (see 21 CFR 201.100(b)(5)); or

- (4) the product is an oral dosage form or a topical preparation and it contains one or more inactive ingredients not customarily used in such product.

Differences that result from compliance with a compendial standard or an FDA requirement will not cause a product to be subject to this exception.

- 5. Initiating regulatory action against an unapproved prescription drug product covered by Part B above, if after November 13, 1984, a change is made in:
 - A. the product's formulation (as described below);
 - B. the product's dosage or strength;
 - C. the product's dosage form;
 - D. the product's route of administration;
 - E. the product's indications for use; or
 - F. the product's intended patient population.

A formulation will be considered different, if:

- (1) the product contains a different active ingredient;
- (2) the product contains a different quantity of an active ingredient;
- (3) the product is a non-oral dosage form other than a topical preparation and it contains one or more different inactive ingredients, different amounts of inactive ingredients, or different proportions of inactive ingredients to the extent that the name, amounts, or proportions of inactive ingredients are required by regulation to be disclosed in labeling (see 21 CFR 201.100(b)(5)); or

- (4) the product is an oral dosage form or a topical preparation and it contains one or more inactive ingredients not customarily used in such a product.

Changes that are made to comply with a compendial standard or an FDA requirement will not cause a product to be subject to this exception.

- * 6. Initiating regulatory action against an unapproved drug product if a manufacturer, packer, or distributor fails to keep records or make reports regarding adverse drug reactions as required by Section 301.305. *

Aside from the exceptions mentioned above, the agency will adhere to the priorities as established. In addition, the * CDER * will deny FDA approval for contract purchase by other Federal government agencies (DOD, VA, PHS) of any drug subject to this policy which does not have an approved NDA or ANDA.

* Material between asterisks is new or revised *

Based on final rule published in Federal Register of 9/2/86 (51 FR 1476)

Issued: 10/6/76 as 7132c.08

Revised: 4/1/81, 9/19/84, 5/8/87, 3/95

Who Is the Manufacturer? Some Additional Considerations for the Multinational

For pharmaceutical manufacturers, large or small, the label must show (as of April 10, 1981) for drugs introduced into interstate commerce for the first time, the name of the sole manufacturer, or the name of the majority manufacturer, plus additional language, or the names of multiple manufacturers. However, there is no federal regulation that requires that the label show the name of the manufacturer if the distributor emplaces its name and address plus truthful language describing its role. Manufacturers or distributors may, however, want to consider state “manufacturer’s name” requirements. The mere insignia of a company’s name and address on the label implies that it is the sole manufacturer. The Drug Enforcement Administration (DEA) registration requirement will be affected by the new regulations of the FDA that require a manufacturer identification and plant and product registration that depart from the former “man-in-the-plant” rule.

Because recent final FDA regulations have made it necessary to clarify registrations of facilities, drugs, and drug products, present registrations under other federal agencies and state administrative agencies should be reviewed to achieve consistency. The FDA regulations took effect in April 1981 for most purposes (FR Vol. 45, No. 74, April 15, 1980, pursuant to Section 502 of the FFDC Act, revising 21 CFR 201, 207, 314).

Formerly, a firm was permitted to claim to be manufacturer of a drug product on the basis of having placed quality control staff in the plant of a subcontrac-

tor. *Man-in-the-plant* refers to contractual arrangements utilized by some drug manufacturers, whereby a firm leases another firm's equipment and labor, and places one or more supervisory personnel in the leased plant to oversee operations. In the past, the labels of drugs produced under these arrangements usually indicated that the drug was manufactured by the contracting firm, making no mention of the contract firm's involvement.

A proposed FDA regulation published on October 3, 1978, revoked the man-in-the-plant labeling policy. The proposal listed ten manufacturing steps generally crucial to the production of drug products. For a firm to represent itself as the sole manufacturer of a product, it would have to perform *all* of the listed steps needed to make the labeled product. If the firm did not perform each requisite function, and yet chose to identify itself as a manufacturer, it would have to list itself as a joint manufacturer along with other firms that performed one or more of the various functions.

The agency also proposed to amend the drug registration and listing regulations: (1) to prohibit an owner or operator of a drug establishment from registering the establishment, if any part of the establishment is registered by any other owner or operator; and (2) to require that any change made in a registered establishment firm name made within 6 months of the registration of the establishment be supported by a signed statement of the establishment's owner-operator that the change is not made for the purpose of changing the name of the manufacturer under 21 CFR 201.1. Another effect of the regulations is that a separately incorporated subsidiary cannot claim to be the manufacturer if the plant or equipment used in the manufacturing process is owned or leased by the subsidiary's parent corporation.

In response to the proposal, FDA received over 50 comments, some of which raised difficult issues about the purpose and consequences of the proposal. Commentors argued that firms that had previously contracted out the manufacture of certain drug products would, when faced with the proposed disclosure requirement, abandon contract manufacturing and, instead, either do the work in their own plants or buy out the generic firms' plants. They also argued that contract arrangements promote flexibility and efficiency, keep costs down, and thereby ultimately benefit consumers. The proposed requirements, in their view, would discourage such arrangements.

Reopening the comment period on the man-in-the-plant regulation, the FDA requested that industry and other interested parties provide detailed information on:

- The extent of and incentives for contract manufacturing
- How the proposed changes might reduce such incentives
- The extent to which this might lead to reduced use of contract manufacturing
- How costs, competition, and prices might be affected

The notice contained specific questions intended to elicit evidence and comments sufficiently relevant and factual to help the agency determine whether or not the proposal would have an anticompetitive effect.

It would appear that most manufacturers who previously utilized man-in-the-plant contract arrangements have either modified these or changed their labeling to include the name of the contract firm. There is no evidence, on the other hand, of widespread shifts to terminate other kinds of contract arrangements on which the supposed anticompetitive effects would depend.

A change in procedures, issued in October 1978, called for the FDA to inspect the operations of not only the lessor firm, but also all other firms using the facility.

FINAL REGULATION

FDA views are, of course, detailed in full in the preamble to the final regulation published in the *Federal Register*, Tuesday, April 15, 1980. This final regulation is an amendment of 21 CFR 201, the labeling regulations, which are intended to effectuate Section 502 of the FDC Act (misbranding provisions).

PART 201—LABELING

1. By revising §201.1 to read as follows:

§201.1 Drugs; name and place of business of manufacturer, packer, or distributor.

(a) A drug or drug product (as defined in §320.1 of this chapter) in finished package form is misbranded under section 502(a) and (b)(1) of the act if its label does not bear conspicuously the name and place of business of the manufacturer, packer, or distributor.

This paragraph does not apply to any drug or drug product dispensed in accordance with section 503(b)(1) of the act.

Thus, it must bear conspicuously the name and business location of the manufacturer, packer, or distributor, except in the case where the drug is being dispensed pursuant to a prescription.

(b) As used in this section, and for purposes of section 502(a) and (b)(1) of the act, the manufacturer of a drug product is the person who performs all the following operations that are required to produce the product: (1) mixing, (2) granulating, (3) milling, (4) molding, (5) lyophilizing, (6) tableting, (7) encapsulating, (8) coating, (9) sterilizing, and (10) filling sterile, aerosol, or gaseous drugs into dispensing containers.

As previously proposed, the manufacturer to be listed singularly is one who performs all applicable operations of the ten listed manufacturing functions.

(c) If no person performs all of the applicable operations listed in paragraph (b) of this section, no person may be represented as manufacturer except as follows:

(1) If the person performs more than one-half of the applicable operations listed in paragraph (b) of this section and acknowledges the contribution of other persons who have performed the remaining applicable operations by stating on the product label that “Certain manufacturing operations have been performed by other firms.”; or

(2) If the person performs at least one applicable operation listed in paragraph (b) of this section and identifies by appropriate designation all other persons who have performed the remaining applicable operations, e.g., “Made by (Person A), Filled by (Person B), Sterilized by (Person C)”;

(3) If the person performs at least one applicable operation listed in paragraph (b) of this section and the person is listed along with all other persons who have performed the remaining applicable operations as “joint manufacturers.” A list of joint manufacturers shall be qualified by the phrase “Jointly Manufactured By __,” and the names of all of the manufacturers shall be printed together in the same type size and style; or

A company that performs any six of the ten functions can show itself as manufacturer and state on the label that “certain manufacturing operations have been performed by other firms.” A company that performs at least one manufacturing function can list individual parties and their individual function; or it can simply list all who had a part in manufacturing the product and use “Jointly manufactured by,” putting all names after it in equal type size and style. This does not preclude a logo or traditional color scheme or type style for the label.

(4) If the person performs all applicable operations listed in paragraph (b) of this section except for those operations listed in paragraph (d) of this section.

(d) The Food and Drug Administration finds that it is the common practice in the drug industry to contract out the performance of certain manufacturing operations listed in paragraph (b) of this section. These operations include: (1) soft-gelatin encapsulating, (2) aerosol filling, (3) sterilizing by irradiation, (4) lyophilizing, and (5) ethylene oxide sterilization.

If the manufacturer does all applicable operations except these, it can name itself solely as the manufacturer.

(e) A person performs an operation listed in paragraph (b) of this section only if the operation is performed, including the performance of the appropriate in-process quality control operations, except laboratory testing of samples taken during processing, as follows:

(1) By individuals, a majority of whom are employees of the person and, throughout the performance of the operation, are subject to the person’s direction and control;

- (2) On premises that are continuously owned or leased by the persons and subject to the person's direction and control; and
- (3) On equipment that is continuously owned or leased by the person.

To be credited as performing a manufacturing function set out in (b) above, the person must do it including the required in-process quality controls, under the following conditions:

1. The majority of the employees are hired by and subject to the direction and control of the named manufacturer.
2. The premises are owned by or continuously leased by the named manufacturer.
3. The equipment is owned by or continuously leased by the named manufacturer.
4. Laboratory testing may be done by contract.

Particular attention should be paid to the use of the word "continuous." The intent is not to permit sharing of facilities by sequential leasing to different manufacturers, even though it may be argued that leasing was "continuous" over the period that a particular lot was manufactured. It remains to be seen whether the courts will find that the particular wording correctly states the intent.

(f) The name of the person represented as manufacturer under paragraph (b) or (c) must be the same as the name of the establishment (as defined in §207.3(b) of this chapter) under which that person is registered at the time the labeled product is produced. In addition, the name shall meet the requirements of paragraph (g) of this section.

Persons named as manufacturer on the label must be the same as on the plant and product registrations.

(g) The requirement for declaration of the name of the manufacturer, packer or distributor shall be deemed to be satisfied, in the case of corporation, only by the actual corporate name, which may be preceded or followed by the name of the particular division of the corporation. A separately incorporated subsidiary shall use its actual corporate name and not the name of its parent company. However, if it chooses, a separately incorporated subsidiary may also identify its parent corporation. Abbreviations for "Company," "Incorporated," etc., may be used and "The" may be omitted. In the case of an individual, partnership, or association, the name under which the business is conducted shall be used.

If a corporation, it must be the actual corporate name, preceded or followed by division name if desired (X Company, Division of Y Corporation); or, if a separately incorporated subsidiary, it must use its own corporate name and may

additionally identify its parent (Z Labs Inc. may be followed by Division of ___, or other appropriate designation of the parent company).

(h) (1) Except as provided in this section, no person other than the manufacturer, packer, or distributor may be identified on the label of a drug or drug product.

(2) The appearance on a drug product label of a person's name without qualification is a representation that the named person is the sole manufacturer of the product. That representation is false and misleading and the drug product is misbranded under section 502(a) of the act, if the person is not the manufacturer of the product in accordance with this section.

Any name that appears on a label, if unqualified, represents the sole manufacturer, and if that is not so, it will misbrand the label for untruth.

(3) If the names of two or more persons appear on the label of a drug or drug product, the label may identify which of the persons is to be contacted for further information about the product.

If more than one name is given, the label *may* identify the one who will answer for further information.

(4) If a trademark appears on the drug or drug product label or appears as a mark directly on the drug product (e.g., tablet or capsule), the label may identify the holder or licensee of the trademark. The label may also state whether the person identified holds the trademark or is licensee of the trademark.

If a trademark appears on the drug form or label, the label *may* identify the owner of the mark or the status of the mark's user.

(5) If the distributor is named on the label, the name shall be qualified by one of the following phrases: "Manufactured for __," "Distributed by __," "Manufactured by __ for __," "Manufactured for __ by __," "Distributor: __," "Marketed by __." The qualifying phrases may be abbreviated.

(6) If the packer is identified on the label, the name shall be qualified by the phrase "Packed by __," or "Packaged by __." The qualifying phrases may be abbreviated.

(i) The statement of the place of business shall include the street address, city, state, and zip code. For a foreign manufacturer, the statement of the place of business shall include the street address, city, country, and any applicable mailing code. The street address may be omitted if it is shown in a current city directory or telephone directory. The requirement for inclusion of the zip code shall apply to consumer commodity labels developed or revised after July 1, 1969. In the case of nonconsumer packages, the zip code shall appear either on the label or the labeling (including the invoice).

(j) If a person manufactures, packs, or distributes a drug or drug product at a place other than the person's principal place of business, the

label may state the principal place of business in lieu of the actual place where such drug or drug product was manufactured or packed or is to be distributed, unless such statement would be misleading.

(k) Paragraphs (b), (c), (d), (e), and (f) of this section, do not apply to the labeling of drug components.

(l) A drug product is misbranded under section 502(a) of the act if its labeling identifies a person as manufacturer, packer, or distributor, and that identification does not meet the requirements of the section.

This section repeats the misbranding threat for omission or mistake or falsification of identification required hereunder.

(m) This section does not apply to biological drug products that are subject to the requirements of section 351 of the Public Health Services Act, 42 U.S.C. 262.

PART 207—REGISTRATION OF PRODUCERS OF DRUGS AND LISTING OF DRUGS IN COMMERCIAL DISTRIBUTION

2. By revising §207.20(a) to read as follows:

§207.20 Who must register and submit a drug list.

(a) Owners or operators of all drug establishments, not exempt under section 510(g) of the act or Subpart D of this Part 207, that engage in the manufacture, preparation, propagation, compounding, or processing of a drug or drugs are required to register and to submit a list of every drug in commercial distribution (except that listing information may be submitted by the parent, subsidiary, and/or affiliate company for all establishments when operations are conducted at more than one establishment and there exists joint ownership and control among all the establishments). Such owners or operators are required to register and to submit a list of every drug in commercial distribution (except that listing information may be submitted by the parent, subsidiary, and/or affiliate company for all establishments when operations are conducted at more than one establishment and there exists joint ownership and control among all the establishments), whether or not the output of such establishment or any particular drug so listed enters interstate commerce, except that drug listing is not required at this time for the manufacturing, preparation, propagation, compounding, or processing of animal feed (including a feed concentrate, a feed supplement, and a complete animal feed) bearing or containing an animal drug. No owner or operator may register an establishment, if any part of the establishment is registered by any other owner or operator.

21 CFR 207.20(a) now reads in regard to registration and submission of a drug list as follows:

Any owner or operator who is not exempt under Section 510(g) must register.

Anyone who does any act in regard to a drug that meets the ten manufacturing criteria in 21 CFR 201.1(b) must register and submit a list of every drug in

commercial distribution, unless it is done by someone involved with them in joint ownership and control of a related establishment. No feed manufacturing establishment needs to be registered. Only one registrant per establishment is permitted.

3. By revising §207.26 to read as follows:

§207.26 Amendments to registration

Changes in individual ownership, corporate or partnership structure location or drug-handling activity, shall be submitted by Form FD-2656 (Registration of Drug Establishment) as amendment to registration within 5 days of such changes. A change in a registered establishment's firm name within 6 months of the registration of the establishment is required to be supported by a signed statement of the establishment's owner or operator that the change is not made for the purpose of changing the name of the manufacturer of a drug product under Section 201.1 of this chapter. Changes in the names of officers and directors of the corporations do not require such amendment but must be shown at time of annual registration.

Mere changes in corporate officers or directors do not necessitate amendment of registration. Changes within 6 months of the former registration must carry a signed statement that it has not been a change of ownership for the purpose of changing the name of the manufacturer on the label. Form FD-2656 should be used to amend registration, within 5 days, for all changes in manufacturer's business structure, name, location, or activity.

PART 314—NEW DRUG APPLICATIONS

4. By revising §314.8(a)(6)(ii) to read as follows:

(a)***

(6)***

(ii) There are no changes from the conditions of the approved application except for a different and suitable proprietary name of the drug (if one is used) and the name and address of the distributor as used on the label and labeling. The name of the distributor shall be accompanied by a qualifying phrase permitted under §201.1(h) of this chapter.

The supplemental NDA is changed to coincide with the required label changes.

Effective date. This regulation shall be effective April 10, 1981, for drugs and drug products initially introduced or initially delivered for introduction into interstate commerce. It also extends the effective date of §201.100(e) which requires that prescription drug labeling bear the name and place of business of the manufacturer, packer, or distributors, to April 10, 1981.

April 10, 1981 is the effective date for drugs initially introduced or initially delivered for introduction into interstate commerce. This means that after that

date the manufacturing entity should not ship into its pipeline of distribution or to a customer directly a drug or drug product with noncompliant labeling.

Current good manufacturing practices may be seen to affect the development as well as the production of pharmaceuticals inasmuch as the regulations apply with equal force to investigational drugs, new drugs, or old drugs that will enter interstate commerce.

Recognition that the genericization of many standard pioneer brands has in some instances compromised the promise of bioavailability and bioequivalence has caused the FDA to issue new regulations in such respect that are closely entwined with the CGMPs.

Those current bioequivalence/bioavailability regulations, which became effective May 28, 1993, incorporated within and set out in 21 CFR 312, 314, and 320, require the retention of reserve samples of the drug products used in the studies submitted in support of the approval of new drug applications (NDAs) and abbreviated new drug applications (ANDAs), for specified periods, and require release such to the FDA on their request. The regulations suggest punishment in the form of refusal to approve or withdrawal of such approval should the regulatee refuse to permit an inspection of facilities or records, or provide reserve samples on FDA request relative to bioavailability and bioequivalence testing. These tougher regulations, reaction to some publicized instances of fraud where samples of the pioneer product were used to support the generic product's claim, apply not only to manufacturers who conduct in-house bioavailability and bioequivalence testing but also to entrepreneurial outside testing facilities operating under contract to conduct such tests for others.

The requirement also applies to foreign-based manufacturers who conduct their own studies for new drug product approval and to foreign testing facilities under contract for a U.S. manufacturer or foreign manufacturer (text available for inspection in Appendix D).

FOR MANUFACTURERS OF BIOLOGICALS

In 1995, the FDA issued a rather detailed and helpful indication of its views as to changes to be reported for Product and Establishment License Applications (60 FR 17535). The FDA emphasized the intent that it was a narrow guideline intended only to provide manufacturers of licensed biological products guidance on changes in manufacturing procedures and establishments that may be implemented with and without prior approval by the Director, Center for Biologics Evaluation and Research (CBER). The guidance document does not apply to manufacturers of whole blood, blood components, source leukocytes, and source plasma. Nor does it address labeling changes.

Therefore, it is obviously intended to clarify the regulatory mechanism found in the regulations under Section 601.12 (21 CFR 601.12), and to diminish

the delays and workload of effectuating the “changes to be reported” burden described.

For domestic and multinationals who are defined as “manufacturers,” these references to the thinking of the Center for Biologics Evaluation and Research may be helpful and have been added to Appendix D.

Recommended: See Appendix D as to an explanation by CBER concerning these issues.

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Other GMPs

The formalization of good manufacturing practices commenced in the 1960s and they are now in effect in over 100 countries ranging from Afghanistan to Zimbabwe. Many countries have not developed local requirements and rely on the World Health Organization Good Manufacturing Practices for Pharmaceutical Products. Regional requirements have also appeared with application to several countries. Examples of these include:

- (a) Pharmaceutical Inspection Convention (PIC) Guide to Good Manufacturing Practice for Pharmaceutical Products—Austria, Denmark, Finland, Hungary, Ireland, Liechtenstein, Norway, Portugal, Romania, Sweden, Switzerland, and the United Kingdom.
- (b) Association of South-East Asia Nations (ASEAN)—Good Manufacturing Practice: General Guidelines—Brunei, Indonesia, Malaysia, Philippines, Singapore, and Thailand.
- (c) European Economic Community (EEC)—Guide to Good Manufacturing Practice for Medicinal Products—Belgium, Denmark, France, Germany, Greece, Ireland, Italy, Luxembourg, the Netherlands, Portugal, Spain, the United Kingdom, and more recently Austria, Finland, and Sweden.

Over the years these regulations/guides have also been supplemented by descriptive guidelines providing additional information on specific topics.

In general, GMPs have been issued as guides to the achievement of consistent product quality, with interpretation and individual variations being accepted. This was always considered by industry to be the best approach, rather than defining specific “how to” regulations. However, within the FDA areas of compliance, the variability of interpretation by individual inspectors, coupled with the authority to delay approvals of submissions because of noncompliance, has raised some questions about the viability of this approach. Obviously, “how to” regulations leave little room for interpretation and therefore in theory make it easier to assure compliance. However, this is a very restrictive approach and does not allow freedom to introduce alternative and more effective methods without modification to the regulations. Consequently, concept or intent regulations are still preferred.

In order to view the CGMPs in the context of an international industry we are presenting brief evaluations of some other GMPs—European, WHO, and Canadian—and highlighting major differences from the CGMPs.

Bulk pharmaceuticals were dealt with in [Chapter 14](#).

GOOD MANUFACTURING PRACTICE FOR MEDICINAL PRODUCTS IN THE EUROPEAN ECONOMIC COMMUNITY

The principles and guidelines for good manufacturing practice are defined in two directives: Directive 91/356/EEC for human products and Directive 91/412/EEC for veterinary products. The Guide to Good Manufacturing Practice applies to both human and veterinary medicinal products, although 2 of the 12 annexes apply specifically to veterinary medicinal products. The CGMPs also apply to both product types.

The preamble to the Guide indicates that this replaces any national GMP requirements within the European Economic Community; consequently, these are multinational requirements, unlike the CGMPs that only apply to products manufactured in or for the United States. There are currently 15 member countries: Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, the Netherlands, Portugal, Spain, Sweden, and the United Kingdom. It also states that alternative approaches are permitted if they are validated and provide equivalent levels of quality assurance. An equivalent situation exists with the CGMP requirements. However, interpretation by individual FDA inspectors and opportunity to block approvals via the Pre-Approval Inspection have made this a less than ideal situation in the United States.

This Guide does not apply to the manufacture of active ingredients, and manufacturers were recommended to apply the 1987 EFTA Pharmaceutical Inspection Convention (PIC) “Guidelines for the Manufacture of Active Pharmaceutical Ingredients.” This guideline was the first published and accepted for

actives and has also been incorporated into the World Health Organization GMPs. More recently (1995) the European Community issued a draft updated guideline for BPCs, and this was reviewed in [Chapter 18](#). The CGMP situation is more confusing, with §211.1 specifically stating that the regulations apply only to drug products (i.e., dosage forms) but with the FDA evaluating at least the final stages of BPC preparation, against these regulations.

Each of the nine chapters of the EEC Guide opens with a principle that essentially defines the intent. The guidelines that follow provide more details on the areas to be addressed. This is an admirable approach and one that one of the authors has used in drafting internal company quality standards. The Guide also includes 12 annexes, which address in even more detail special areas such as sterile medicinal products, biological medicinal products and liquids, and creams and ointments.

In reviewing the Guide, only those topics that differ from the FDA regulations are addressed.

CHAPTER 1. QUALITY MANAGEMENT

The principle emphasizes that the achievement of quality requirements “is the responsibility of senior management and requires the participation and commitment by staff in many different departments and at all levels within the company.” This clearly acknowledges the important role of senior management and that quality control alone cannot achieve the required results.

The chapter also refers to product development and requires the application of GMP and GLP to the design and development phase. The CGMPs do not specifically address design and development, although GLPs do apply to certain stages and there is an expectation that GMPs will be applied especially during production of clinical supplies.

Self-inspection and/or quality audit is required; these are not specifically included in the CGMPs. There is also the statement that materials may not be released for use before the relevant tests are performed. The term “relevant” is very subjective and could be considered to allow use at risk provided some data were available. This is similar to §211.84, which uses the term “appropriate.”

CHAPTER 2. PERSONNEL

The concept of the *qualified person*, with responsibility for product release, is introduced. Unlike §211.22 the qualifications and experience required for this head of QC are defined (Article 23 of Directive 75/319/EEC).

A formal qualification is required in pharmacy, medicine, veterinary medicine, chemistry, pharmaceutical chemistry, or biology. The subjects that must be included in the course are defined. The qualification is to be followed with 1 year

of practical training, at least 6 months of which is to be in a pharmacy. A further 2 years of experience in a quality control environment is required.

This chapter also differentiates between the evaluation of products imported from other EEC countries and those from non-EEC countries. In the latter case, the importing country must perform full qualitative analysis, quantitative analysis of all active ingredients, and any other tests required to confirm product quality. Directive 75/319/EEC Article 22 does allow Member States to relieve the importing qualified person of these responsibilities provided further exportation is not to occur and that arrangements have been made with the exporting country to assure that the testing was performed there. For importation from another EEC country, this testing is not required if the quality control reports, signed by the qualified person, are provided.

The chapter defines the responsibilities of the head of production and the head of QC. This clearly makes the head of production responsible for production operations and compliance with procedures. This role is not specified in the CGMPs, and §211.25 only requires that personnel shall be appropriately qualified and/or experienced to perform their assigned duties. This defined role for production is a positive acknowledgment of the importance of product management in the GMP compliance.

In addition to defining the areas of responsibility for the heads of these two key functions, there is a definition of joint responsibilities, which can include approval of procedures, process validation, approval of suppliers, and monitoring of GMP compliance.

With respect to training there is a requirement to assess effectiveness. This should be a routine requirement for any important activity.

All personnel, presumably only those more directly involved in production and support activities, are to be medically examined at the time of recruitment. Section 211.28 does refer to personnel health and medical examination, but there is no specific requirement for a medical examination on recruitment or at any other specified time.

CHAPTER 3. PREMISES AND EQUIPMENT

The maintenance and repairs to premises are to be performed so that there is no adverse impact on quality. This would seem to be obvious. However, §211.58 only requires that buildings shall be maintained in a good state of repair. For equipment, the Guide and the CGMPs are essentially equivalent.

The Guide requires that highly sensitizing products (e.g., penicillins) and “certain additional products such as certain antibiotics, certain hormones, certain cytotoxins, certain highly active drugs and non-medicinal products” should be produced in different facilities or exceptionally by campaigning in the same facilities. Section 211.176 applies restrictions only to penicillin.

Sampling of starting materials is normally expected to be performed in a separate sampling area, but alternatives are allowed provided they prevent the opportunity for cross-contamination. It is surprising that this elaboration is included since the Guide overall allows alternatives. Section 211.84 does not specify a separate area but does require the prevention of contamination.

CHAPTER 4. DOCUMENTATION

This chapter makes several references to the signing of documents—approvals, alterations, process steps (initials), process completion, process deviations. There is also reference to electronic recording, which is considered acceptable with the usual safeguards regarding access. This would appear to be equivalent to the approach now being prepared by the FDA and included as a Proposed Rule in the *Federal Register* of August 31, 1994, pp. 45160–45177.

There is a rather extreme requirement for the use of log books—for recording of equipment validation, calibration, maintenance, cleaning and repair, and also for equipment and facility usage. The only reference to log books in CGMPs is §211.182 with respect to equipment cleaning and maintenance. Possibly of minor significance, the Guide refers to log books and CGMPs only to logs.

CHAPTER 5. PRODUCTION

There are several references to minimizing the potential for cross-contamination, ranging from material sampling through production, from operator clothing to packaging. The CGMPs address most of the same concerns except that with the exception of penicillin there is no specific reference to the manufacturing processes themselves.

Although validation appeared to gain European acceptance slowly, a requirement now appears.

The importance of starting material quality is emphasized by the preference to buy directly from the producer rather than through an agent. Although not included in the CGMPs, this is a good practice.

The preference for roll labels over cut labels is emphasized. The FDA has been more demanding in this area due to the number of recalls caused by incorrect labeling. The Guide also emphasizes the need to confirm that code readers and counters are working correctly. Again there is a specific highlight, probably because of the importance of the subject.

The samples removed from packaging lines are not to be returned. The intent of this is to prevent mix-ups by the return of opened/modified units to the wrong line. There would seem to be no need for this restriction provided adequate precautions are taken; also, is a side table adjacent to a packaging line considered to be part of the line? The CGMPs provide no such restrictions.

The Guide also notes that “reprocessing of rejected products should be exceptional.” While not so described in the CGMPs, the FDA and industry would agree. Indeed, a validated process should only rarely produce rejects.

CHAPTER 6. QUALITY CONTROL

Storage of reference samples for products differs from that for starting materials. The Guide suggests that with certain defined exceptions (solvents, gases, and water), samples of all starting materials should be retained for 2 years after the expiration date of the last batch of product manufactured from the material. The CGMPs (§211.170) refer to retained samples of active ingredients only and for 1 year beyond product expiration.

The testing reports require the initials of persons performing and checking the testing and signatures for release. The earlier comments on electronic recording presumably also apply here. This is equivalent to §211.194.

CHAPTER 7. CONTRACT MANUFACTURE AND ANALYSIS

With the emphasis on ISO 9000 in Europe, it is not surprising that a chapter was included on contractual arrangements.

The contract should define responsibilities with respect to purchasing of materials, testing and release of materials, process control, final testing, and product release. Additional issues include who retains samples and evaluates complaints. The drafting of the contract should involve persons with adequate knowledge, especially of GMP requirements.

Access to the contractor’s premises should be agreed in the contract.

The CGMPs do not include any reference to contract operations. The emphasis on technical involvement in the Guide is particularly relevant since many contracts are drafted by legal departments with only limited technical input.

CHAPTER 8. COMPLAINTS AND PRODUCT RECALL

The Guide provides more direction on the extrapolation of complaints to other batches. The Guide and the CGMPs both require regular review of complaints data to identify potential problems and require appropriate action. The Guide also provides additional guidance with respect to recalls but these are essentially identical to FDA expectations.

CHAPTER 9. SELF-INSPECTION

Self-inspections are to be conducted by competent persons within the company and are to be recorded. The author considers that additionally managers and su-

pervisors should perform frequent audits of their functions—and these need not necessarily be recorded.

Surprisingly, the CGMPs do not include any reference to internal inspections—which are, however, performed and expected.

The 12 annexes, providing more detailed information, are entitled Manufacture of sterile medicinal products; Manufacture of biological medicinal products for human use; Manufacture of radiopharmaceuticals; Manufacture of veterinary medicinal products other than immunologicals; Manufacture of immunological veterinary medicinal products; Manufacture of medicinal gases; Manufacture of herbal medicinal products; Sampling of starting and packaging materials; Manufacture of liquids, creams and ointments; Manufacture of pressurized metered dose aerosol preparations for inhalation; Computerized systems; and Use of ionizing radiation in the manufacture of medicinal products.

Copies of “The Rules Governing Medicinal Products in the European Community. Volume IV. Good Manufacturing Practice for Medicinal Products” may be obtained from Unipub, 4611-F Assembly Drive, Lanham, MD 20706-4391, USA (301-459-7666).

WORLD HEALTH ORGANIZATION—GOOD MANUFACTURING PRACTICES FOR PHARMACEUTICAL PRODUCTS

The first WHO guide on GMPs was drafted in 1967. Some minor revisions were incorporated when it was published as a Supplement to the International Pharmacopoeia in 1971. It was later incorporated into the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce (WHO 28.65) in 1975. No further revisions occurred until 1992. This latest version took into account the considerable developments in GMPs since 1975 and also the ISO 9000 series and the Convention for Mutual Recognition of Inspection in Respect of the Manufacture of Pharmaceutical Products (PIC).

The WHO GMPs are presented in three parts: Part One, “Quality management in the drug industry: philosophy and essential elements”; Part Two, “Good practices in production and quality control”; and Part Three, containing two supplementary guidelines. It is anticipated that this part will be expended by the addition of more guidelines. The attachment of the guidelines to the GMPs makes the document easier to use, whereas the FDA Guides and Guidelines are totally separate.

Throughout the document there is considerable emphasis on validation and avoidance of cross-contamination. The WHO guideline is essentially identical in content to the EEC guideline. This means that there is a high level of consistency throughout a large part of the industry.

GENERAL CONSIDERATIONS

The guide is applicable to all “large-scale operations for the production of drugs in their finished dosage forms including large-scale processes in hospitals and the preparation of clinical trials supplies.” “Large-scale” is not defined but the term is used presumably to differentiate production that is usually for multiple patient/customers from dispensing and individual patient special preparations. The specific reference to hospitals is unique. Other GMP guides/regulations do not specifically refer to hospital manufacture. It is possibly assumed that they should comply but hospitals are rarely, if ever, inspected.

Parts One and Two (the main body of the GMPs) do not apply to the manufacture of active ingredients (bulk pharmaceutical chemicals). However, one of the two supplementary guidelines in Part Three does deal specifically with this subject. This is a welcome plus compared with the confusion over the degree of application of the CGMPs to bulk pharmaceutical chemicals. Excipients are not covered by the current guide, and this topic could become a subject for a future Part Three guideline.

As with the EEC GMPs, the WHO document is considered to provide guidance, and equivalent alternative approaches are allowed to meet individual needs provided they are validated. There is, however, an interesting footnote—“the world “should” in the text means a strong recommendation.” This implies that even more attention than usual should be given to the evaluation of alternatives in these instances.

Because of the similarity to the EEC guideline, only a limited review is presented.

PART ONE. QUALITY MANAGEMENT IN THE DRUG INDUSTRY: PHILOSOPHY AND ESSENTIAL ELEMENTS

As with ISO 9000, the important role of top management in defining and authorizing quality policy is emphasized. It also states that quality assurance (the concept, not the function) is a management tool. This appears to be indicating that quality should be used as a value-adding approach to the business rather than being considered a regulatory requirement.

1. *Quality assurance.* In this section the guide introduces the term “principle,” with which it opens several later sections. The principle here is that quality assurance is a concept that covers everything that can impact on product quality. It includes all procedures, activities, and personnel responsibilities. It applies to product design and development (as with ISO 9001), although there is no elaboration on this aspect of product life cycle. Presumably it is considered that although design and development can impact on future production and product quality, the GMPs do not apply—except as previously indicated to the production of

clinical supplies. This is consistent with other GMP guides. However, it is stated that pharmaceutical products should be designed and developed with the application of GCP and GLP and to “take into account the requirements of GMP.”

The importance of management is denoted by the need to define managerial responsibilities in job descriptions.

Quality audit and/or self-inspection is required to evaluate compliance. The either/or approach is novel and again is an indication of the wide-reaching role of the supervision and management in assuring compliance and deemphasizing the role of the quality function. (See also section 9.)

The overall purpose of WHO GMP compliance is to ensure that products are “fit for their intended use.” This goes beyond CGMPs, which are primarily concerned that the products should be safe and effective. For example, a bottle that is difficult to open may not be fit for intended use, but the product inside could be safe and effective. It is also stated that many levels of personnel in different functions, plus suppliers and distributors, must participate and be committed to the achievement of the required quality but that the *responsibility* lies with senior management. Recently the FDA has been issuing a greater number of Warning Letters, which are usually addressed to the chief executive officer of the company. One of the main reasons for this was to ensure that top management were aware of important quality deficiencies. However, one would expect that company internal communications would normally address such issues.

2. *Good manufacturing practices for pharmaceutical products (GMP).* The section states that GMPs “are directed primarily to diminishing the risks, inherent in any pharmaceutical production, that cannot be prevented completely through the testing of final products.” This statement clearly acknowledges that perfection may not be achievable. It also infers that infrequent inadvertent lapses in compliance that result in no increase in risk should not be considered a serious issue. The potential risks (not detectable by finished product testing) are identified as cross-contamination and labeling mix-ups. This appears to be a very practical approach, since deviations from specifications can usually be detected by product evaluation.

The subsection on complaints requires that action is taken to prevent recurrence. This is an illustration of quality being used as a tool for improvement. In more far-seeing companies, one would expect the complaint handling process (reactive) to be converted into a proactive customer satisfaction process; possibly this is beyond GMP.

3. *Quality control.* This encompasses all activities that are sometimes subdivided functionally into quality control (laboratory) and quality assurance (procedures and documentation). It is surprising in a modern document, with so many positive approaches, that the quality function is still termed quality control. It is becoming increasingly common for the overall function to be called quality assurance, with quality control being the laboratory activity.

The required independence of quality control from production is emphasized—“is fundamental.” As indicated elsewhere in this book, there are several ways to assure this independence, and functional reporting of plant QC outside of plant management is only one approach.

4. *Sanitation and hygiene.* No issues.

5. *Validation.* Validation is required for processes, testing, and cleaning. There is no reference to computer systems validation. Installation and operational qualification for equipment are not mentioned, but these could be considered subsets of process validation. The terms prospective and retrospective validation are included, but not concurrent validation. While it is acknowledged that in most situations retrospective (currently marketed products) and prospective (new products) validation will apply, there are situations where concurrent validation is appropriate. These were described earlier in the book.

6. *Complaints.* The emphasis relates to the potential for recall.

7. *Product recalls.* Unlike the CGMPs, there is a requirement to test the recall system to ensure that it will function effectively if needed.

8. *Contract production and analysis.* ISO 9000 was probably the underlying basis for this section, which requires that the responsibilities of each party are clearly defined and agreed with respect to purchasing, testing, and releasing materials, for process controls and product testing, and also for record keeping. This is an important subject requiring special attention from the quality function since contracts are frequently handled by the legal department, which is not always aware of these important technical considerations.

There is a specific comment that the contract should permit audit of the contractor operation. The author has seen examples where this was not included and audit was either prohibited or restricted.

There is no equivalent section in the CGMPs.

9. *Self-inspection and quality audits.* This section elaborates on the general statement in section 2 and thereby brings a different interpretation to the subject. The author has previously defined self-inspection as an inspection carried out by the management/supervision responsible for the particular process or activity. In this section self-inspection relates to the use of an internal multifunctional team to assess compliance. Quality audit is defined as an approach to improve performance of a process using external sources. While this can be an effective approach, the absence of continuous self-inspection by management weakens the concept that all personnel are to be involved in quality.

A subsection refers to audit of suppliers' facilities—but only if required. However, it is difficult to appreciate how GMP compliance can be assured without an audit by someone, either from the purchaser's company or a regulatory agency that issues a report. Possibly ISO 9000 certification could be acceptable confirmation that quality systems are in place.

10. *Personnel*. This section is essentially the same as outlined in the EEC guide. The scientific education requirements are defined for key supervisors and managers of manufacturing and quality control. These include an appropriate combination of chemistry or biochemistry, chemical engineering, microbiology, pharmaceutical sciences and technology, pharmacology and toxicology, physiology, or other related sciences. They must also have experience in the manufacture and quality assurance of pharmaceutical products. The individual responsibilities of the heads of production and quality control and their shared responsibilities are also identified. The CGMPs do not go into this amount of detail.

Training programs are to be approved by the head of production or quality control, as appropriate, and effectiveness should be assessed. There is no reference to the qualifications of the personnel giving the training. This is the converse of the CGMPs, which do not refer to approval of programs but do require training to be given by “qualified individuals.”

Personal hygiene requirements again mirror the EEC guideline. Preemployment health examination is required, and also periodic eye examinations for those who perform visual inspections. It is surprising that color blindness evaluations are not specifically mentioned especially for laboratory personnel.

11. *Premises*. The main differences from the CGMPs relate to the identification of products (in addition to penicillin) that require self-contained or separate facilities. These include biological preparations (live organisms), some other antibiotics, hormones, cytotoxic substances, and highly active pharmaceutical products and nonpharmaceuticals. It is accepted that campaign production in the same facilities may be satisfactory provided there are validated cleaning procedures.

There is also a recommendation, usually followed in the design of newer facilities, that services should be accessible from outside the manufacturing areas to facilitate maintenance.

12. *Equipment*. No issues.

13. *Materials*. Suppliers are to be named in the specifications and, where possible, purchases should be directly from the manufacturer. The objective here is to eliminate the possibility of an intermediary agent changing source of supply without the knowledge of the purchaser. This is established practice but is not in the CGMPs. It is also recommended that the material specification be “discussed” with the supplier. This, although a move in the right direction, is not enough. Specifications should be agreed with the supplier.

As with most GMPs, materials must be released by quality control before use. However, this does not appear to preclude use before all testing is completed, provided quality control give approval.

The important subject of reference standards is also addressed in this section and allows the use of secondary (in-house) standards. These should be cross-checked against official reference standards—a good practice for laboratory operations.

14. *Documentation.* The importance of good documentation as a solid basis for GMP compliance is emphasized. This section does, however, introduce some degree of confusion with respect to signatures on documents. For example, 14.3 requires documents to be signed, while 14.9 indicates that electronic data-processing systems may be used for data entry. Is a signature data? In 14.28, on processing records, there are several references to requirements for signatures or initials, whereas in 14.31 on packaging records the required entries may be by signature or electronic password. Overall it must be assumed that a secure and validated electronic system is considered an adequate alternative to handwritten signatures and initials. This subject is undergoing resolution by the FDA.

Logbooks are required for major pieces of equipment to record validation, calibration, maintenance, cleaning, and repair. In today's electronic age we assume that electronic records would be acceptable but this is not so stated.

PART TWO. GOOD PRACTICES IN PRODUCTION AND QUALITY CONTROL

This part goes into more detail on the procedures to be followed. Sterile products and bulk pharmaceutical chemicals are covered in Part Three.

15. *Good practices in production.* This section has an emphasis on the avoidance of contamination and highlights the need for effective cleaning between products, the segregation of hazardous operations, and the minimization of dust generation and potential problems of air recirculation.

A unique point (15.18) is the requirement to clean all containers before filling to eliminate any foreign contamination such as glass particles. This would seem excessive, however, as previously indicated alternative approaches are acceptable. Consequently, provided it can be demonstrated that foreign materials will not be present, the cleaning could be eliminated. It must be noted that the cleaning requirement is a "should"—a strong recommendation.

In the subsections on processing operations, it states that instruments used for analytical testing should be checked daily in addition to routine calibration. Although not specified in CGMPs this is probably a useful approach, especially for instruments located in processing environments.

There are the usual concerns about the potential for labeling mix-ups. The guide does not go as far as the current FDA approach in defining what to do, but it does recommend labeling immediately after filling and sealing and taking special care with cut labels, off-line coding, and hand packaging. The use of on-line electronic scanning is encouraged, and the need to routinely verify the operational effectiveness of such equipment is noted.

16. *Good practices in quality control.* As previously indicated, in this guide quality control is the complete quality function, encompassing quality control and quality assurance functions.

Certificates of analysis from a supplier may be used as a basis for reduced testing, but there are several interesting and practical provisos—reliability of the supplier's analytical capability must be demonstrated by comparative analysis, the supplier's site must be audited, and the certificate must be an original (not a photocopy) and include a statement of the specification and the test methods used plus the results and date of testing. This goes well beyond the CGMPs. Most of the points make practical sense. However, the need for original certificates is difficult to understand unless it is to minimize the chance of fraud. The date of testing does ensure that the data are current.

The evaluation of batch failures or process deviations should not only be investigated but should, if necessary, be extended to include other batches or other products. This should be normal practice within the industry but is not specifically included in CGMPs.

The requirements for retention samples of active ingredients and products are the same as for the CGMPs. The WHO guide also has a retention requirement for excipients: with the exception of solvents, gases, and water, these are to be retained for 2 years.

PART THREE. SUPPORTING AND SUPPLEMENTARY GUIDELINES

17. Sterile pharmaceutical products. The introduction states that this is a supporting guideline and does not replace any sections of Part One or Part Two. Again the emphasis is on minimizing the risk of contamination—microbial, particulate, and pyrogen.

There are no surprises in this section, which is very similar to the EEC guideline. There is reference to the use of barrier technology and automated systems that “can produce significant advantages in ensuring the sterility of manufactured products.” There is a specific point that a conveyor should not pass through a partition from a Class 100 area into an area with a lower classification unless the conveyor is continuously sterilized.

Disinfectants and detergents are to be monitored for microbial contamination, but there is no specific requirements that they should be sterile.

The bioburden impact is to be evaluated, including starting materials and product, before sterilization. Routine evaluation of materials can be eliminated if supported by data.

The subject of aseptic processing versus terminal sterilization is briefly raised, and terminal sterilization is to be used wherever possible. Where this is not possible, “consideration should be given to complementing the filtration process with some degree of heat treatment.” These sentiments are commendable but unless some further guidance is provided or regulatory agencies rely on the

individual company evaluation, this could lead to excessive amounts of evaluation and delays in product registration. Some of the issues include:

How much degradation is acceptable when terminal sterilization or complementary heating are used?

The amount of toxicology work to evaluate the potential impact of these degradation products.

Which heat treatments should be evaluated to complement aseptic processing (temperature and time).

Filled containers of injections are required to be inspected individually. This is also a USP requirement. This is another area where process improvements and validation have not allowed any relaxation of evaluation. Presumably the facts that no process can provide 100% assurance of compliance, the evaluation is nondestructive, and the product is an injection all contribute to the continuation of this test.

CANADIAN GOOD MANUFACTURING PRACTICES. THIRD EDITION (1989)

The introduction emphasizes the guideline nature of this document: “the content of this publication should not be regarded as the only interpretation of the regulations for Good Manufacturing Practice” and “Manufacturers and importers may use this guideline as a basis for the elaboration of specific requirements appropriate to their individual needs.”

The guideline only applies to dosage forms and there is no reference to any alternative approaches for drug substances:

The overall format of the guideline is interesting. The regulations, which are statutory requirements, are highlighted and are then followed by the rationale for the regulation and an interpretation with more detail of how compliance might be assured. This appears to be a very sensible and practical approach.

In May 1995 some additional draft “interpretations” were issued for review.

The general intent is similar to other major GMPs and only unique points will be addressed.

PREMISES (C.02.004)

The 1989 document made no reference to critical systems. This has been addressed in the 1995 proposals, which require such systems as HVAC and DI water to be qualified when installed or changed and to be subject to periodic verification.

EQUIPMENT (C.02.005)

Some details are included that, while obvious, are not in other GMPs.

Tanks used for the manufacture of liquids and ointments are to be equipped with fittings that can be dismantled and cleaned.

Wooden equipment should not come into contact with materials or product.

Chain drives should be enclosed.

Tanks and hoppers should have covers.

Use of tape for repairs should be avoided.

Validation is introduced in the 1995 proposal by requiring installation and operational qualification on all critical manufacturing equipment—“critical” is not defined. Also, design and maintenance of equipment to assure effective operation is extended to process water systems.

PERSONNEL (C.02.006)

The heads of quality control and manufacturing should have university, or equivalent, science degrees and relevant practical experience. This is not as detailed as the EEC and WHO guidelines but is more extensive than the CGMPs.

The regulators have identified that the cutbacks occurring in industry could have a detrimental impact on quality, and the 1995 proposal states that “the responsibilities on any one individual are not so intense as to risk quality.” Evaluation of training effectiveness is also required.

SANITATION (C.02.007)

The proposed update requires validation of cleaning procedures.

RAW MATERIAL TESTING (C.02.009/C.02.010)

As with the other regulations, testing is expected to be complete before material is used in production. The accuracy and precision of noncompendial methods are to be determined. These are two key elements of analytical method development. However, linearity, specificity, and robustness are not mentioned.

Some reliance on the material suppliers analytical data is allowed—reduced testing. The conditions and requirements are defined in the interpretation. Five consecutive lots from the supplier must have been tested and found to be in compliance with the specifications. The dosage-form manufacturer may then perform only an identity test, provided there was no potential for deterioration during transportation. The dosage-form manufacturer should perform full testing every fifth lot, or two lots per year. If any lot is rejected, the supplier must be requalified.

ISO 9000 certification is proposed as an alternative way to qualify suppliers. In these circumstances confirmatory testing may be performed annually.

Brokers and other intermediaries are also included in the update, since each container of bulk raw materials repackaged after leaving the site of manufacture is to be sampled and identity-tested prior to release.

MANUFACTURING CONTROL (C.02.011/C02.012)

The batch records are to include the initials of personnel performing each production step. This is one of a few references to initials. Although there is no elaboration with respect to electronic identification, it seems most likely that the alternative approaches accepted in general by the Health Protection Branch (HPB) would apply here.

Printed packaging materials are to be “readily distinguishable” to minimize the potential for mix-up. There is no additional guidance on what is suitable.

Validation of critical production processes and changes is required in the proposed update. In this instance “critical” is defined—those processes that can cause variation. The use of validated on-line label accountability systems is also proposed as an alternative to label reconciliation.

When subcontracting takes place, the contract should define acceptable quality performance and GMP responsibility.

A self-inspection program is required. There should be written reports of the findings and the corrective actions initiated. While inherent in most pharmaceutical operations, self-inspection is noticeably absent in the CGMPs. One of the authors has previously published a paper emphasizing the importance of an additional inspection—the daily informal checking by management and supervision. This does not require written reports, unless the observations are serious and require some wide-ranging corrective action, but immediate verbal feedback is essential.

The HPB does on occasion ask to see copies of self-inspection reports. Industry has argued that these should be confidential internal reports in order to maximize their benefit. Otherwise they could become a focal point for inspectors to identify and cite deficiencies that have already been identified and corrected. Previously the FDA has indicated that it would only view these inspection reports if it found other evidence of serious compliance deficiencies. More recently some investigators have been asking to see them as proof that internal inspections were being performed.

The HPB prefers that companies confirm the suitability of contract manufacturers by inspection. However, alternative approaches are allowed if an inspection is not practicable. The alternatives include evaluation of the plant master file, evaluation of regulatory inspection reports, or evaluation of the manufacturer’s own corporate inspection reports. This subject is not specifically ad-

dressed in the CGMPs, but most companies do use one or more of these approaches.

QUALITY CONTROL DEPARTMENT (C.02.013/C.02.014/ C.02.015)

There is nothing novel or unusual in this section except for a point of detail: the person in charge of the laboratory must be “an experienced university graduate holding a degree in science related to the work carried out . . . or reports to a person having these qualifications.” While this would seem to be self-evident, there could be some problems in a company that performs both chemical and microbiological laboratory work when two such qualified individuals may be required, depending on their qualifications and experience.

The emphasis on validation in the update is further demonstrated by the requirement for a change control process—an essential element of validation.

PACKAGING MATERIAL TESTING (C.02.016/017)

Testing and reduced testing requirements are the same as described earlier for raw materials.

FINISHED PRODUCT TESTING (C.02.018/019)

The rationale emphasizes that due to limitations of sampling techniques, finished product testing complements the in-process controls. This is very sensible and clearly highlights the importance of in-process controls. Taken to a logical conclusion, it should then be possible to delete some finished product tests, which are more effectively performed during the production process—these would include tablet weight, thickness, hardness, fragility, and liquid volume checks.

The accuracy and precision of nonpharmacopeial methods are to be evaluated. This falls short of full validation and does not include verification to confirm the adequacy of any method in a new facility.

An importer must perform testing on receipt of product. However, reduced testing is allowed, with the conditions being equivalent to those required for the reduced testing of raw materials. There is some similarity to the EEC guidelines, which require full testing for products produced outside of the EEC. The CGMPs do not address this use of contract production, and the regulations only require that the product should have been tested.

Although no changes are included in the update, it is noted that the Health Protection Branch (HPB) is “generally dissatisfied with the level of third party compliance.”

RECORDS (C.02.020–C.02.024)

Some of the record requirements for importers are unique. An importer must have records demonstrating GMP compliance by the manufacturer. This may be achieved by inspection of the manufacturer or via the alternative approaches outlined in C.02.012 above. An importer must also be able to provide the HPB with the results of testing performed on raw materials and packaging materials. Presumably these can be obtained from the manufacturer if requested.

Self-inspection records are to be retained for at least 3 years. This topic is frequently discussed in the industry, and one view (outside of Canada) has been that if the action points have all been completed, the reports could be discarded after the next inspection.

SAMPLES (C.02.025/026)

A sample of each lot of raw material used in the production of dosage forms is to be retained for at least 2 years after the lot was last used. This is very different from the CGMPs, which require retention samples of active ingredients only, not excipients. Also, the normal retention time is 1 year after the expiration of the dosage form in which it was last used—for a product with a 5-year shelf-life this would relate to 6 years. Since the primary value of retention samples is in the evaluation of quality queries on the dosage form, the FDA retention period seems more appropriate.

The Canada regulation also requires the sample to be retained in Canada, with the manufacturer or the importer. Such a restriction is not imposed by the CGMPs.

The recent FDA pronouncements on electronic documentation/identification are reflected in the update. Electronic batch records are considered acceptable, and electronic signatures may be used provided the procedures are validated and secure.

STABILITY (C.02.027/028)

The interpretation section provides additional detail on the requirements to determine product shelf-life. Accelerated data must be supported by ambient data and at least two lots (now changed to three) must be evaluated. This detail is not in the CGMPs but is incorporated into the ICH guidelines for new products, where three batches are required and the length of storage is defined.

The update incorporates the ICH stability testing requirements for both new products and significant changes.

There is a statement that sterility testing of a sterile formulation may not be required if the effectiveness of the container-closure system has been demonstrated.

STERILE PRODUCTS (C.02.029)

This section provides additional details with respect to sterile products. The interpretation does indicate that terminal steam sterilization is the method of choice for sterilization when practical. This is in line with the FDA thinking but is not in the CGMPs. It is also proposed that the holding time between manufacture and sterilization should not exceed 24 hours “unless suitable precautions are taken.” This is lower than occurs in practice in many operations, but again it is a guideline, not a regulation.

The update has followed FDA direction in requiring terminal (steam) sterilization unless it causes degradation. There is no mention of the use of alternative (less stressful) heat treatment. There is also no reference to unacceptable physical factors, such as plunger expulsion in prefilled syringes.

Aseptic processing that excludes human contact is allowed as an alternative to steam sterilization. This applies to form-fill-seal technology and should presumably also apply to barrier/isolation technology.

Compounding is allowed in Grade D areas provided it is performed in closed vessels.

APPENDICES

Three appendices are included: Medical Gases, Plant Master Files, and Medicated Premixes. These are not reviewed here.

GENERAL PROPOSED CHANGES

The update also indicates that the HPB inspectors expect to see a validation master plan. It is also noted that until Canadian guidelines are available for cleaning validation and sterilizer validation, the FDA and ICH guidelines can be used.

Importers must obtain full batch records from their suppliers at least once per year.

Other Approaches to Quality

In recent years quality has become recognized as a business differentiator. The initial stimulation, especially in the United States, was the immense adverse impact on the U.S. automotive and electronics industries from Japanese imports. The United States had a large home market with minimal external competition. This lack of competition was essentially due to three factors: the cheap-labor countries, which included Japan, were not capitalized for major items such as automobiles or televisions and had a reputation for cheap but poor-quality goods; the European countries, which were recovering from the devastating impact of two wars, were mainly high-labor-cost areas, but some luxury products were exported to the United States; and third, the distances from Europe and Japan resulted in high transportation costs. This all changed, with much support and direction from an American, W. Edwards Deming, when the Japanese realized that to expand their economy by exporting they must change the international perception of poor quality and that higher and consistent quality actually costs less, due to higher output and less rework activity. This, coupled with the acceptance of a long-term view with respect to profitability, forever changed the role of quality in business. Another factor having significant impact was that products were becoming more sophisticated and consequently more complex to manufacture, and even low levels of poor quality in individual components would result in a high level of poor quality in the finished product.

The American public started to buy the more reliable Japanese imports, and eventually American industries realized that they too must adopt quality concepts if they intended to stay in business. Over the years, most of the quality improvement tools that were developed were introduced by major companies. These included quality circles, zero defects, statistical process control, quality function deployment, etc. These rarely succeeded since in most cases they were introduced as stand-alone techniques that were expected to resolve all the problems of the company. As each new concept came to light it was introduced with tremendous support and enthusiasm, usually by consultants—who did become successful—and the previous techniques waned. The major change in the United States came about when it was realized that quality improvement should apply to every business activity and should be integrated into the business strategy—total quality. Within the United States the government got involved and, in order to enhance attention to quality, introduced in 1987 the Malcolm Baldrige National Quality Award (MBNQA). The Japanese have the Deming Award.

Within Europe there was also the realization that quality was important. Additionally, with the unification of Europe through the European Economic Community, it was considered that there should be some guiding principles that would allow for easy intercountry distribution knowing that each country was following an equivalent approach to quality. The internal application of these principles might also make it more difficult for others to import into the EEC. As a consequence the EEC introduced the International Standards Organization Series 9000 (ISO 9000).

The various approaches described in this book can be summarized as:

MBNQA—a tool for business improvement through product and service quality

ISO 9000—a process for assuring consistent material and product quality via contractual arrangements

GMPs—compliance programs designed to identify key activities that can impact on consistent product quality.

This chapter addresses the MBNQA and ISO 9000 approaches to quality management and identifies key differences from CGMPs.

MALCOLM BALDRIGE NATIONAL QUALITY AWARD

The MBNQA is an annual award to recognize business excellence and quality achievement of U.S. companies. The award program, which was introduced in 1987, is the responsibility of the Department of Commerce and is managed by the National Institute of Standards and Technology. The Award promotes:

Awareness of quality as an increasingly important element in competitiveness.

Understanding the requirements for performance excellence.

Sharing of information on successful performance strategies (best practices) and benefits derived from implementation of these strategies.

Awards may be presented in three categories: manufacturing companies or subsidiaries, service companies or subsidiaries, and small businesses (companies with not more than 500 full-time employees).

The MBNQA is an award program, unlike the other programs described in this book, which are compliance programs. Both MBNQA and ISO 9000 recognize and reward achievement by the award or certification, whereas GMP evaluations punish noncompliance. Most companies adopting the MBNQA approach do so with the aim of ultimately winning an award and the extensive visibility and prestige that results. Also, while winning an award does not guarantee success (one winner has gone out of business), most of the winners have shown significant business improvements such as speed to market with new products, increased market share, productivity increases, and growth in sales and profits. *Business Week*, October 18, 1993, stated that the three publicly traded, whole-company Baldrige winners outperformed Standard and Poor's 500 from time of winning until September 30, 1993, by 8.6 to 1. However, only a limited number of awards are given each year, and companies using the MBNQA approach should do so with the primary aim of helping to drive business success.

The award is based on a set of core values and concepts that are designed to integrate customer satisfaction and company performance. These include customer-driven quality, leadership, continuous improvement and learning, employee participation and development, fast response, design quality and prevention, long-range view of the future, management by fact, partnership development, corporate responsibility and citizenship, and, not least, results orientation.

These core values and concepts are then incorporated into the seven categories that are evaluated in an application (see [Figure 1](#)). These are:

1. *Leadership*. This is the overall driver of the process. This "category examines senior executives' personal leadership and involvement in creating and sustaining customer focus, clear values and expectations, and a leadership system that promotes excellence. Also examined is how the values and expectations are integrated into the company's management system, including how the company addresses its public responsibilities and corporate citizenship." Although going far beyond any GMP requirements, the role of senior managers as drivers of improvement is universal.

The FDA is concerned that senior management are not sufficiently involved in quality compliance and that they may, in some instances, not even be aware

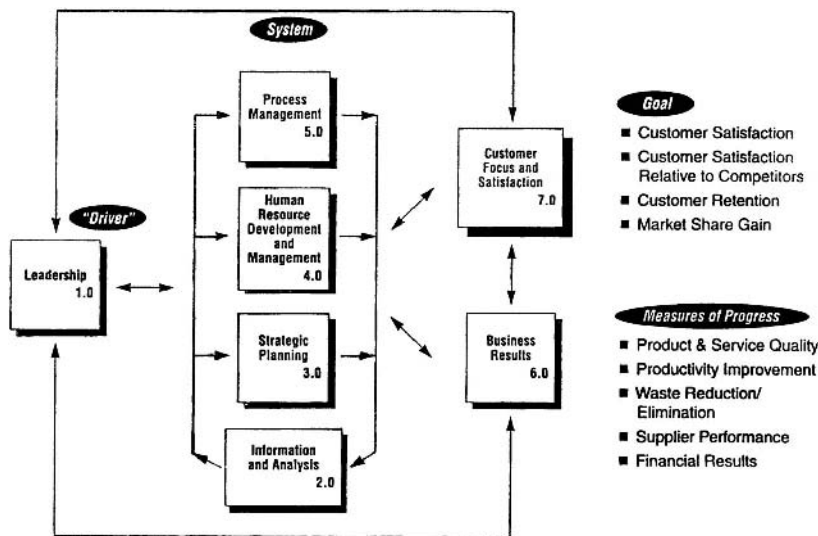


Figure 1 Baldrige Award criteria framework, dynamic relationships.

of serious quality issues within their companies. This resulted in an increase in the number of Warning Letters issued with respect to quality deficiencies. These Warning Letters are addressed to the company CEO—the rationale being that this will guarantee the availability of any resources needed to correct the deficiencies.

2. *The system.* This comprises four supporting processes:

(a) Information and analysis, which “examines the management and effectiveness of the use of data and information to support customer-driven performance excellence and marketplace success.” Within the pharmaceutical industry, especially within plant operations, significant amounts of data are generated. More use could be made of this data to drive improvements.

The FDA does expect to see data analyzed to identify trends and where necessary result in appropriate remedial activity. The annual report is one example where all product quality data is reviewed and reported. An excellent use of the annual review would be to incorporate the data, along with process changes that occur, into a “living” product quality document. This document would contain the original validation protocol, data, and approval; all significant process changes and the decisions regarding the need for revalidation; the annual quality reports and actions taken; all revalidation processes and data; customer feedback data; and production performance.

(b) Strategic planning “examines how the company sets strategic directions, and how it determines key plan requirements. Also examined is how the

plan requirements are translated into an effective performance management system.” Strategic planning is not an element in GMPs. However, FDA investigators will sometimes take into account a company’s plan for improvement when deciding what action to take on finding a compliance deviation.

(c) Human resource development and management “examines how the work force is enabled to develop and utilize its full potential, aligned with the company’s performance objectives. Also examined are the company’s efforts to build and maintain an environment conducive to performance excellence, full participation and personal and organizational growth.” This coincides with a current trend for flatter organizational structures, delegation of responsibility, and use of self-managed work teams. The FDA appears to be unhappy with this direction with respect to quality, where tight control by a QA/QC department is preferred and expected. The pharmaceutical industry is still grappling with this issue—on how to gain the maximum benefits from delegation without adversely impacting on product quality or safety.

The consistent achievement of product quality standards and compliance with regulatory requirements will be enhanced by the awareness by all employees of the importance of these issues. Only when every employee is fully committed to the achievement of consistent quality and held accountable and rewarded will real progress be made. The introduction of self-directed work teams as a means of involving all employees in quality has had some success. The team takes responsibility for all or most elements of the work activity. This can include hiring, dismissal, and disciplinary action, production scheduling, work hours, and even product quality. A QC function can only examine a limited sample of production and consequently the possibility of detecting low-frequency defects is small. However, the production team is exposed to a much larger sample and consequently is in a better position to detect, and correct, problems. Policing has never been an effective way to achieve compliance, although a high level of enforcement activity coupled with significant penalties can have some major impact. This has been illustrated by the drinking and driving laws in Scandinavia, where this approach has had a dramatic impact.

(d) Process management “examines the key aspects of process management, including customer-focused design, product and service delivery processes, support services and supply management involving all work units, including research and development. The Category examines how key processes are designed, effectively managed and improved to achieve higher performance.”

Unlike the GMPs, this goes into both product design and product distribution service. While the latter may not be too important to product quality and efficacy, the design stage is critical. A poorly designed product could be difficult to produce to a consistent quality. The inherent process variability could result in failures of individual units to fully comply with the defined specifications.

Product delivery service is obviously crucial for business success. Failure

to deliver the right product on time with the correct paperwork (invoices, etc.) will soon result in loss of customers. Delivery service also includes the process for dealing with trade customer queries.

3. *Measures of progress.* The “category examines the company’s performance and improvement in key business areas—products and service quality, productivity and operational effectiveness, supply quality, and financial performance indicators linked to these areas. Also examined are performance levels relative to competitors.”

When initially introduced, the MBNQA did not address the impact on business performance. This has now changed significantly, with Business Results and Customer Focus and Satisfaction results comprising 41% of the total possible score (410 out of 1000).

The GMPs are not directly concerned with business performance, and evaluation of measures is usually directed toward compliance issues such as rejections, reworks, and complaints as indicators of inadequately validated production processes and process deviations as the examples of system noncompliance. In fact, FDA investigators frequently visit the reject area early in an inspection in order to identify failures. They can then go back into the respective batch records to evaluate the cause and to establish whether adequate remediation activity had been initiated. An important role for QA/QC is to provide senior management with data to demonstrate positive business improvements resulting from quality-related activities. The concept of benchmarking—comparison with competitors—is also introduced in this category. The measures of success also go beyond the usual financial indices, which are essentially historical, and includes operational performances, which are indicators of future financial success.

This is essentially a new arena for QA/QC professionals. Previously they have focused on the narrow areas of technology and regulations—areas where they were acknowledged as professionally capable and responsible. These new areas require the establishment of new sources of data (benchmarking) with clear definition of the metrics used and the ability to communicate and influence management in these business-related areas. QA/QC management must earn respect in these new areas so that they will be heard and so that appropriate improvement actions will be initiated.

4. *Goal.* The overall goal of the process is business success through customer satisfaction. The category of customer focus and satisfaction “examines the company’s systems for customer learning and for building and maintaining customer relationships. Also examined are levels and trends in key measures of business success—customer satisfaction and retention, market share, and satisfaction relative to competitors.”

As previously indicated, GMPs do not address business success or results. The only measure of customer satisfaction included is customer dissatisfaction—customer complaints. As previously noted in the relevant section of the GMPs

(§211.198), this is of limited value as a measure of customer satisfaction. If the ease of obtaining feedback from customers improves, the level of complaints may increase. The use of “800” telephone numbers on products has proven this fact. However, evaluation of complaints can identify key areas for improvement that should be acted upon.

Details of the examination criteria are shown in [Figure 2](#). The evaluation of applications for the award involves four steps:

Stage 1: independent review of the application by at least five examiners.

Stage 2: consensus review and identification of suitable candidates for Stage 3.

Stage 3: site visits to companies with sufficiently high scores to essentially confirm the accuracy of the submitted data. In some ways this is equivalent to the FDA Pre-Approval Inspection.

Stage 4: judges’ review of the applications, its review by the examiners, site visit report, and inspector recommendations.

The system used for the evaluation of applications is to examine each category with respect to:

Approach—the design of the process, its relevance, incorporation of improvement cycles, innovation

Deployment—use throughout the organization

Results—performance measures are defined, data demonstrate improvement, benchmarking is used.

Companies not intending to apply for the Award could find the MBNQA process to be a valuable tool in helping to improve business performance based on quality improvement and customer satisfaction. Useful benchmarking data and best practices information can be obtained via the extensive communications resulting from each award cycle or by direct interaction with other companies. Internal self-assessment can also provide useful data, since minimum scores required to be considered for an award are known.

Copies of the MBNQA criteria, along with application forms and instructions, can be obtained from Malcolm Baldrige National Quality Award, National Institute of Standards and Technology, Route 270 and Quince Orchard Road, Administration Building, Room A537, Gaithersburg, MD 20899-0001, USA.

ISO 9000 SERIES

The ISO 9000 standards were published in 1987 by the International Standards Organization, based in Switzerland. The series was designed as a means to increase customer confidence in the quality of supplied materials, products, or

1995 Examination Categories/Items	Point Values
1.0 Leadership	90
1.1 Senior Executive Leadership.....	45
1.2 Leadership System and Organization.....	25
1.3 Public Responsibility and Corporate Citizenship.....	20
2.0 Information and Analysis	75
2.1 Management of Information and Data.....	20
2.2 Competitive Comparisons and Benchmarking.....	15
2.3 Analysis and Use of Company-Level Data.....	40
3.0 Strategic Planning	55
3.1 Strategy Development.....	35
3.2 Strategy Deployment.....	20
4.0 Human Resource Development and Management	140
4.1 Human Resource Planning and Evaluation.....	20
4.2 High Performance Work Systems.....	45
4.3 Employee Education, Training, and Development.....	50
4.4 Employee Well-Being and Satisfaction.....	25
5.0 Process Management	140
5.1 Design and Introduction of Products and Services.....	40
5.2 Process Management: Product and Service Production and Delivery.....	40
5.3 Process Management: Support Services.....	30
5.4 Management of Supplier Performance.....	30
6.0 Business Results	250
6.1 Product and Service Quality Results.....	75
6.2 Company Operational and Financial Results.....	130
6.3 Supplier Performance Results.....	45
7.0 Customer Focus and Satisfaction	250
7.1 Customer and Market Knowledge.....	30
7.2 Customer Relationship Management.....	30
7.3 Customer Satisfaction Determination.....	30
7.4 Customer Satisfaction Results.....	100
7.5 Customer Satisfaction Comparison.....	60
TOTAL POINTS	1000

Figure 2 1995 Award examination criteria.

services. This was especially important for trade between different countries with different languages and cultures. Not surprisingly, the initial emphasis was within the European Economic Community as part of the movement to a unified market.

The series consists of five standards: ISO 9000, ISO 9001, ISO 9002, ISO 9003, and ISO 9004. The American National Standards Institute (ANSI) is the

U.S. representative of ISO and has adopted the series as the ANSI/ASQC Q90 series.

The ISO 9000 series focuses primarily on the product (which may be a service, material, or product) and its development and production; the only emphasis on end customer relates to procedures for complaints. There is now some pressure, especially from larger companies, to extend the series to include marketing, sales, and customer service.

ISO 9000 has gained extensive acceptance, having been adopted by about 80 countries. Compliance is voluntary; however, some companies have made certification a condition of doing business. Companies can be registered as in compliance with any of the three main standards (ISO 9001, 9002, or 9003). The registration process involves independent audit and confirmation that quality systems are in compliance with the standard. A fee is involved and periodic re-inspection is required. A certificate of compliance is provided. This is the converse of the CGMP situation, where compliance is assumed unless the FDA states otherwise—and no certificate of compliance is provided.

Neither the CGMPs nor ISO 9000 includes measures of effectiveness with respect to product quality. It is implied that compliance with procedures will improve product quality. A survey referenced in the *Financial Times* (September 20, 1994) indicated that most companies became certified because of pressure from industry customers rather than an urge to improve quality. Initial criticisms have been that the certification process is too costly in terms of consultant fees and management time and that it had become a “licence to trade” rather than a quality improvement tool. A comment attributed to David Martin, from the UK Federation of Small Businesses, is that “The whole approach of BS 5750 [the UK equivalent of ISO 9000] has a tendency to make you inward looking. Using it you can produce lousy products very efficiently.”

The success of any quality improvement process requires intelligent introduction and application. It must be integrated into the business plan and focused on the achievement of measurable improvements in defined areas. Much of the criticism about ISO 9000 relates to its introduction only as a means of obtaining certification rather than as an improvement tool.

However, a major benefit of ISO 9000 has been to allow and encourage nonregulated industries to introduce a quality management system. Previously the only widely established systems included regulations such as GMPs aimed at specific industries and award programs such as Deming and Malcolm Baldrige. None of these had universal coverage, although the World Health Organization GMPs do apply to many countries. Since the pharmaceutical industry is already subject to quality regulations, the introduction of ISO 9000 has been somewhat limited, with most emphasis by the manufacturers of bulk pharmaceutical chemicals.

ISO 9000: “QUALITY MANAGEMENT AND QUALITY ASSURANCE STANDARDS”

ISO 9000 defines terms and provides overall guidance on the selection and application of the three main standards (ISO 9001, 9002, 9003). It is, like ISO 9004, a descriptive document and is not part of the registration/certification process. There are four parts. ISO 9000-1, “Guidelines for selection and use,” provides guidance on which standard to use. ISO 9000-2, “Generic guidelines for the application of ISO 9001, ISO 9002 and ISO 9003,” provides guidance on implementation. ISO 9000-3, “Guidelines for the application of ISO 9001 and the development, supply and maintenance of software,” deals specifically with computer software applications. ISO 9000-4, “Guide to dependability programme management,” provides guidance when the emphasis is on product or service reliability.

ISO 9001, 9002, and 9003 are alternative standards that can be applied in different business situations. They are not progressive steps to a more comprehensive program but are stand-alone standards with specific applications and emphasis.

ISO 9001: QUALITY SYSTEMS—MODEL FOR QUALITY ASSURANCE IN DESIGN, DEVELOPMENT, PRODUCTION, INSTALLATION, AND SERVICING

The emphasis is on product design and the main application is to those contractual arrangements that involve product design and development in addition to production, installation, or servicing; it applies also where product requirements are defined in functionality or performance terms. The design and production of customized packaging or third-party development and production of OTC medicines could be addressed by this standard.

Key points from the quality system requirements (section 4) are highlighted next.

“Management Responsibility” (4.1, 4.1.1, 4.1.2, 4.1.2.1, 4.1.2.2, 4.1.2.3, 4.1.3)

The involvement and commitment of top management is required in defining quality policy and objectives. This is not a specific requirement of CGMPs but is assumed. The evaluation of costs associated with quality objectives is expected. This does appear to encourage a cost/benefit analysis. Such an evaluation is not included in the CGMPs, where there is an implied assumption that 100% compliance is required regardless of cost. However, when new FDA regulations are promulgated, a financial impact evaluation is performed. Also, in the event of a

quality failure in the marketplace the remedial activity agreed with the FDA does take into account risk (safety).

Although there is no definitive requirement for a QC/QA function, the responsibilities and authority of all who manage, perform, or verify work affecting quality are to be defined. There is also reference to those personnel who must have organizational freedom to address quality issues—equivalent to the quality control unit in §211.22. A manager must be appointed with responsibility for ensuring the continuing compliance of the quality system and reporting performance. Section 211.22 refers to the QC review of production records but does not specifically refer to overall review/audit of all quality related procedures, although this is done via internal quality audit.

“Quality System” (4.2, 4.2.1, 4.2.2, 4.2.3)

A documented quality system is to be implemented and maintained, usually in the format of a quality manual. A life-cycle approach is proposed to include all relevant elements from market research to define customer requirements through product design and development, process planning and development, purchasing, production or provision of services, verification, packaging, technical assistance and servicing, after sales, and final disposal or recycling after use.

Most of these topics are included in the CGMPs. The major differences relate to the initial identification of customer needs and subsequent product development and the after-sales and disposal issues. GMPs tend to be more concerned with product safety and efficacy than with customer satisfaction. ISO 9004 provides more extensive guidance on the quality system and addresses the subject of quality costs—economic issues not included in CGMPs. The system is expected to measure costs in the areas of prevention, appraisal, internal failure, and external failure. This information provides focus for further improvement activity and can demonstrate positive financial benefits from the successful application of the system. An effectively validated process, required by CGMPs, should result in only low levels of quality costs since rejections, reworks, and recalls should also be infrequent. There could still be low levels of customer satisfaction resulting from inadequate product design criteria. Again the FDA would expect to see corrective actions resulting from high and continuing levels of customer complaints.

“Contract Review” (4.3, 4.3.1, 4.3.2, 4.3.3, 4.3.4)

A contract should exist that clearly defines the quality requirements and assures that the supplier has the capability of meeting these requirements. CGMPs (§211.80) refer to procedures for receipt, identification, storage, handling, sampling, testing, and approval/rejection of materials and components. There is no specific reference to supplier contracts. For bulk drug substances the CGMPs

apply, so it may be assumed that these suppliers do have appropriate quality systems in place. The situation with respect to excipient suppliers is less clear, and these suppliers do not necessarily have adequate procedures, nor are they subject to regular inspection by the FDA or by their customers. As a consequence, clearly defined quality contracts with excipient suppliers would seem to be essential.

“Design Control” (4.4, 4.4.1–4.4.9)

This section, along with ISO 9004-1, provides extensive guidance with respect to design control. A starting point is the conversion of customer needs into technical specifications for components, processes, and products. Essentially every step in the design/development process is monitored to assure that the final product will meet the agreed design criteria. This level of control during product design and development is not included in CGMPs. Some limited control is exercised in specific areas by the application of GLPs to laboratory operations, GCPs to clinical evaluations, and GMPs to the preparation of clinical trial materials. However, none of these is specifically concerned with the potential impact of product design on product quality or customer satisfaction.

“Document and Data Control” (4.5, 4.5.1, 4.5.3)

This requires the effective control of approved documentation from initiation, issue to use. Obsolete documentation must be removed from the operation and a change control procedure is required. These requirements are essentially equivalent to §211.100.

“Purchasing” (4.6, 4.6.1–4.6.4.2)

This section, supplemented by section 9 in ISO 9004-1, defines how to assure the quality of materials purchased by the supplier; it goes one step further back in the contract/supply chain. It refers to definition of specifications, selection of subcontractors, respective release evaluations to be performed by the supplier and the subcontractor, agreement on test/inspection methodologies, resolution of quality disputes, receiving inspection controls, and retention of records.

CGMPs (§§211.80, 211.82, 211.84, 211.86, 211.122) only address from receipt of purchased materials onwards. However, the other elements in the ISO section are expected to be applied.

“Control of Customer-Supplied Product” (4.7)

The supplier is expected to maintain records of any materials or components received from the customer for incorporation into the supplier’s process. The

supplier is to notify the customer (the subcontractor in this instance) of any deliveries that are lost or unsuitable for use).

Sections 211.84 and 211.122 refer to testing and evaluation of purchased components but do not specifically indicate that the supplier of these components should be informed of deficiencies. However, this is normal business practice, and inclusion in GMP regulations would be superfluous.

“Product Identification and Traceability” (4.8)

This requires traceability of the product by the supplier through the various stages of production, delivery, and installation. This is equivalent to the traceability requirement in §211.184.

“Process Control” (4.9)

This requires that production should be planned and implemented via approved processes, during which there should be appropriate controls. With the exception of production planning, these activities are included in subparts F and G in CGMPs. Inadequate planning can have an adverse impact on quality, especially for “rush jobs” where short cuts may be taken.

ISO 9004-1 (10.2) requires that process capability be determined for production processes. This is a step beyond validation (§211.110) and with the establishment of suitable process capability standards provides a higher level of assurance of consistent compliance with product quality standards—again reducing the costs of quality failure (reworks, rejections, and recalls).

“Inspection and Testing” (4.10, 4.10.1–4.10.5)

The supplier is responsible for assuring the quality of purchased materials/components from subcontractors. As with §211.84, reduced testing by the supplier is acceptable. Unlike CGMPs (§211.84), components may, under certain circumstances, be used before completion of all testing. This is a very practical situation. Similar flexibility is not permitted for the product from the supplier, where all agreed evaluations are to be completed before distribution.

“Control of Inspection, Measuring and Test Equipment” (4.11, 4.11.1, 4.11.2)

Measuring and test equipment is to be routinely calibrated and appropriate action taken in the event that equipment is found to be outside the accepted ranges. Equivalent to §211.68 and §211.160.

“Inspection and Test Status” (4.12)

This refers to the status identification of materials and products and is equivalent to §§211.80, 211.82, and 211.142.

“Control of Non-Conforming Product” (4.13, 4.13.1, 4.13.2)

Procedures are required for the identification, evaluation, documentation, segregation, and disposition of nonconforming material. The eventual disposition may include reworking, acceptance if the nonconformance will not adversely impact on further processing or quality, regrading for alternate use, or rejection. CGMPs allow only rejection (§§211.80, 211.82, 211.84) or reprocessing of product (§211.115). In practice the ISO approach is frequently used with supporting explanatory documentation.

“Corrective and Preventive Action” (4.14, 4.14.1–4.14.3)

This expands on 4.13 with respect to the action required to correct and prevent future occurrences. Actions recommended include investigation to identify root causes, evaluation of financial implications of the problems and possible resolution, elimination of the cause with changes incorporated into operational documentation, introduction of appropriate controls to monitor the effectiveness of the change, and management review of the overall conclusions. With the exception of the financial impact, these other aspects equate to FDA expectations on evaluation of production problems.

“Handling, Storage, Packaging, Preservation, and Delivery” (4.15, 4.15.1–4.15.6)

This supplier is expected to have adequate procedures for ensuring that the product is received in satisfactory condition by the customer. These elements are also addressed in §211.82 and §211.87.

“Control of Quality Records” (4.16)

This requires the retention of records relating to product quality for an agreed period of time. Section 211.180 defines specific retention times. ISO 9004-1 defines the types of documentation to be retained. These include specifications and test methods, test results, production records, qualification and validation reports, audit reports, calibration data, quality manual, and quality cost reports. This is more detailed than §211.180, which refers to “any production, control or distribution record that is required to be maintained.”

“Internal Quality Audits” (4.17)

Documented internal audits are to be performed, in accordance with a defined plan, to provide assurance of ongoing compliance. Follow-up is required to confirm the completeness and effectiveness of the corrective action.

There is no specific reference to internal audits in the CGMPs, but these are performed and are expected by the FDA.

“Training” (4.18)

Training is required for all personnel engaged in quality-related activities, and records are to be maintained. ISO 9004-1 expands on this by emphasizing job training, retraining, statistics, supervisory training, and the need to make management aware of the operation of the quality system and its measures of effectiveness.

Section 211.25 covers much of the same ground but does not make specific reference to either retraining or creating awareness with senior management. ISO 9004-1 also refers to the importance of motivation, quality awareness, measurement, and recognition of performance. None of these important factors are included in the CGMPs.

“Servicing” (4.19)

This brief section requires that where service is part of a contractual arrangement there shall be procedures to evaluate and report on performance. There is no equivalent requirement in the CGMPs.

“Statistical Techniques” (4.20, 4.20.1, 4.20.2)

Statistical techniques are to be applied to verify process capability and product characteristics. ISO 9004-1 defines possible areas of application: market analysis, product design, stability, process control and capability, sampling, and data analysis. It also suggests possible statistical methodologies: design of experiments and factorial analysis, analysis of variance and regression analysis, tests of significance, quality control charts and cusum techniques, and statistical sampling.

Many of these approaches and applications are used in the pharmaceutical industry but the subject is not addressed in the CGMPs. However, statistical applications are expected with respect to analytical method validation, design and analysis of clinical experiments and data, for the evaluation of stability data, and in some cases for sampling techniques.

ISO 9002: QUALITY SYSTEMS—MODEL FOR QUALITY ASSURANCE IN PRODUCTION, INSTALLATION, AND SERVICING

This standard applies to more routine production where product quality requirements can be adequately expressed in terms of specifications. In these situations design criteria are either unimportant or have been previously resolved. Confidence in supplier processing capability is required. The production and supply of excipients and bulk pharmaceutical chemicals could fit into this standard, which is probably the most extensively applied ISO 9000 standard in the pharmaceutical industry. ISO 9002 is identical to ISO 9001 with the exclusion of the section on design control (4.4, 4.41–4.49).

ISO 9003: QUALITY SYSTEMS—MODEL FOR QUALITY ASSURANCE IN FINAL INSPECTION AND TEST

This applies to contractual arrangements that rely on a supplier's ability to detect and control nonconforming products by final testing or inspection. It is difficult to perceive a situation where this would apply within the pharmaceutical industry—where quality must be built into the design and production of the product. One possible situation could be for the evaluation of production with a low level of defectives where inspection is used to cull out the defective units.

The standard is a condensed version of ISO 9002 with exclusion of specific sections which do not apply: purchasing (4.6), process control (4.9), servicing (4.19).

ISO 9004: QUALITY MANAGEMENT AND QUALITY SYSTEM ELEMENTS

This descriptive standard, currently in eight parts, provides more detailed guidance on the quality elements included in the registration/certification standards ISO 9001, 9002, and 9003. The eight parts are entitled: 1 Guidelines; 2 Guidelines for services; 3 Guidelines for processed materials; 4 Guidelines for quality improvement; 5 Guidelines for quality plans; 6 Guidelines on quality assurance for project management; 7 Guidelines for configuration management; and 8 Guidelines on quality principles and their application to management practices.

Copies of the ISO 9000 series may be obtained from the American National Standards Institute, 11 West 42nd Street, New York, NY 10036, USA.

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Import and Export of Pharmaceuticals and Other Products Subject to CGMPs

While the great impact of the so-called Cold War has seemingly come to an end, even with the proliferation of partial-world and world agreements aiming at the end of trade barriers, every major manufacturing nation and even many recipient countries have established elaborate systems of export controls and import controls that operate under somewhat varied conditions of enforcement. As an example, the author recalls a recent instance when in seeking a supplier in Europe for an ingredient, the information the U.S.-based corporation would have had to supply could have been deemed in violation of several United States statutes that had been enacted and were being enforced to counter the turnover to international terrorist centers of key chemical manufacturing information. This was the aftermath of indictments by central European authorities.

While giant special agreements, such as the Canada–United States Free Trade Agreement and NAFTA, have wedded pharmaceutical investment opportunities between Canada, Mexico, and the United States, expansion into each by nationally based corporations of any one of these requires considerable current information that must be added to the mix in building and staffing manufacturing and sales organizations. Though Canada and the United States exchange more goods, services, and capital than any other two countries in the world, and though the Canadian regulatory agency and the U.S. Food and Drug authorities cooperate

extensively, enough differences exist to require knowledge and caution on the part of manufacturers in each of the partners.

Notwithstanding the foregoing, Section 801 with its recent amendments remains preclusive of the import of drugs or devices that appear from examination of samples or otherwise to be:

processed, or manufactured or packed under insanitary conditions, or, in the case of a device, the methods used in, or the facilities or controls used for, the manufacture, packing, storage, or installation of the device do not conform to the requirements of Section 520(f), or
it is an article forbidden or restricted in sale in its country of origin, or
it is adulterated or misbranded, or violative of Section 505, it will be refused admission, unless it can meet the requirements set out in Section 801(b) [which essentially require bonding, and reworking and/or relabeling etc.]

One must contrast this with the relatively simpler task for the domestic exporter. For the latter, the newer benevolence of Section 801(d) permits export of drugs violative of Sections 501 and 502 of the Act, as long as it is in accord with Subsections (A), (B), (C), (D), meets the vendee's specifications, doesn't violate the law of the country of destination, has been marked for export only on the outer package label, and is not for sale in the United States. In fact, it cannot come back to the United States after export except for return to the U.S. manufacturer, unless the FDA has given permission.

As to biologics, the law is the same. And the statute also permits export, with compliance as to conditions set by the FDA, of unapproved biologics, as well as unapproved new drugs, new animal drugs, or partially processed biologics (as would be chemical intermediates, to certain designated nations). Must these products meet CGMPs in the United States? Yes, and as with devices, they must not have been banned in the United States and must comport with the general export requirements we have described.

A drug in a bulk package, not in dosage form, used in manufacture of an investigational drug requires a label as per 21 CFR 201.122(b), and the foreign exporter must so label it. When received and incorporated into a final product for IND submission, it cannot further be moved until the IND has been determined suitable under 312 for further dissemination.

As to importing under U.S. Customs Law and regulation for the global manufacture and distributor, insight into and advice on the Harmonized Commodity Description and Coding System are both essential and available. With the expanded use of foreign trade zones, the special labeling requirements for imports, and major enforcement trends of recent vintage, as well as possibilities for exemptions that exist for this industry, there is little doubt that reference materials provided by the U.S. Customs Service and specially informed experts are a must.

EXPORT (FROM THE UNITED STATES) GUIDANCE

Firms exporting products from the United States are often asked by foreign customers or foreign governments to supply a certificate relating to products subject to the Federal Food, Drugs and Cosmetics Act and other acts that the Food and Drug Administration administers. The Food and Drug Administration is the U.S. agency with regulatory oversight of certification. Certification is the process by which a formal or official attestation is made concerning the regulatory status of a product, or the system by which a commodity is manufactured. The certification process may include the issuance of a certificate to accompany the exported product. The following is the FDA Guideline as to Certification for Export.

CHAPTER VIII—IMPORTS AND EXPORTS

SEC. 801. [381] (a) The Secretary of the Treasury shall deliver to the Secretary of Health and Human Services, upon his request, samples of food, drugs, devices, and cosmetics which are being imported or offered for import into the United States, giving notice thereof to the owner or consignee, who may appear before the Secretary of Health and Human Services and have the right to introduce testimony. The Secretary of Health and Human Services shall furnish to the Secretary of the Treasury a list of establishments registered pursuant to subsection (i) of section 510 and shall request that if any drugs or devices manufactured, prepared, propagated, compounded, or processed in an establishment not so registered are imported or offered for import into the United States, samples of such drugs or devices be delivered to the Secretary of Health and Human Services, with notice of such delivery to the owner or consignee, who may appear before the Secretary of Health and Human Services and have the right to introduce testimony. If it appears from the examination of such samples or otherwise that (1) such article has been manufactured, processed, or packed under insanitary conditions or, in the case of a device, the methods used in, or the facilities or controls used for, the manufacture, packing, storage, or installation of the device do not conform to the requirements of section 520(f), or (2) such article is forbidden or restricted in sale in the country in which it was produced or from which it was exported, or (3) such article is adulterated, misbranded, or in violation of section 505, then such article shall be refused admission, except as provided in subsection (b) of this section. The Secretary of the Treasury shall cause the destruction of any such article refused admission unless such article is exported, under regulations prescribed by the Secretary of the Treasury, within ninety days of the date of notice of such refusal or within such additional time as may be permitted pursuant to such regulations. Clause (2) of the third sentence of this paragraph shall not be construed to prohibit the admission of narcotic drugs the importation of which is permitted under the Controlled Substances Import and Export Act.

(b) Pending decision as to the admission of an article being imported or offered for import, the Secretary of the Treasury may authorize delivery of

such article to the owner or consignee upon the execution by him of a good and sufficient bond providing for the payment of such liquidated damages in the event of default as may be required pursuant to regulations of the Secretary of the Treasury. If it appears to the Secretary of Health and Human Services that an article included within the provisions of clause (3) of subsection (a) of this section can, by relabeling or other action, be brought into compliance with the Act or rendered other than a food, drug, device, or cosmetic, final determination as to admission of such article may be deferred and, upon filing of timely written application by the owner or consignee and the execution by him of a bond as provided in the preceding provisions of this subsection, the Secretary may, in accordance with regulations, authorize the applicant to perform such relabeling or other action specified in such authorization (including destruction or export of rejected articles or portions thereof, as may be specified in the Secretary's authorization). All such relabeling or other action pursuant to such authorization shall in accordance with regulations be under the supervision of an officer or employee of the Department of Health and Human Services designated by the Secretary, or an officer or employee of the Department of the Treasury designated by the Secretary of the Treasury.

(c) All expenses (including travel, per diem or subsistence, and salaries of officers or employees of the United States) in connection with the destruction provided for in subsection (a) of this section and the supervision of the relabeling or other action authorized under the provisions of subsection (b) of this section, the amount of such expenses to be determined in accordance with regulations, and all expenses in connection with the storage, cartage, or labor with respect to any article refused admission under subsection (a) of this section, shall be paid by the owner or consignee and, in default of such payment, shall constitute a lien against any future importations made by such owner or consignee.

(d) (1) A food, drug, device, or cosmetic intended for export shall not be deemed to be adulterated or misbranded under this Act if it—

(A) accords to the specifications of the foreign purchaser,

(B) is not in conflict with the laws of the country to which it is intended for export,

(C) is labeled on the outside of the shipping package that it is intended for export, and

(D) is not sold or offered for sale in domestic commerce.

This paragraph does not authorize the exportation of any new animal drug, or animal feed bearing or containing a new animal drug, which is unsafe within the meaning of section 512.

(2) Paragraph (1) does not apply to any device—

(A) which does not comply with an applicable requirement of section 514 or 515,

(B) which under section 520(g) is exempt from either such section,
or

(C) which is a banned device under section 516, unless, in addition to the requirements of paragraph (1), the Secretary has determined that the exportation of the device is not contrary to public health and safety and has the approval of the country to which it is intended for export.

Obviously, products imported for sale and distribution in the United States must accord with the same scientific and legal criteria as do products domestically manufactured. That means they must be produced under CGMPs no less stringent. To ease the potential for challenge, the FDA has a program for voluntary inspection of extranational manufacturing facilities from which the larger volumes of such imports will emanate. It is the responsibility of foreign exporters and/or substantial domestic importers to utilize such background resources. All drugs exported to the United States by foreign firms, like all drugs exported by domestic firms, must be in compliance with U.S. drug listing requirements. Foreign firms, however, need not register as establishments.

The enforcement procedures as to imported products are necessarily somewhat different. To the extent that such products are legally subject to FDA regulation, they are subject to inspection at the time of entry through U.S. Customs. A shipment suspected to contain adulterated material through violation of the CGMPs or otherwise out of compliance with the Federal Food and Drug law and the implementing regulations is subject to detention. The owner or claimant will have opportunity to contest the nonimportability of the product pending the final decision as to whether it must be destroyed, can be returned to the exporter, salvaged, brought into compliance, etc. Besides posting a bond, the importer must stand the expense of having any violations corrected under the supervision of an FDA official.

The regulations add some definition to the persons, sampling, payments, and basis for relabeling and reconditioning imports at 21 CFR 1.83 through 1.99, which are very helpful in understanding the concerns of both the owners or consignees of the proffered materials and those of the government. Regulations as to the U.S. Customs Service duties can be consulted at 19 CFR 1 in this regard as well. It explains costs chargeable in connection with relabeling and reconditioning inadmissible imports.

SUGGESTED READINGS

1. The Drug Exports Amendment Act of 1986 and Chapter Eight of the Federal Food, Drug and Cosmetic Act in general (see Appendix).
2. The Food, Drug and Cosmetic Law Institute maintains an index of articles published in its journal on all subjects.

APPENDIX: IMPORT AND EXPORT GUIDELINES AND FORMS

SUBJECT: Certification for Exports

BACKGROUND

Firms exporting products from the U.S. are often asked by foreign customers or foreign governments to supply a certification relating to products subject to the Federal Food, Drug, and Cosmetic Act and other acts FDA administers. Certification is the process by which a formal or official attestation is made concerning the regulatory status of a product, or the system by which a commodity is manufactured. Requests for certification have variously asked for verification that the products being exported: (1) are freely marketed in the U.S.; (2) are in compliance with U.S. laws and regulations; (3) are in compliance with the importing country's requirements; (4) meet certain national or international standards, such as quality standards; or (5) do not contain specific contaminants. This certification process may include issuance of a certificate to accompany the exported product.

FDA has historically issued a number of different types of certificates, e.g. Certificates of Free Sale, Certificates for Export, Certificates to Foreign Governments, and most recently the European Union (EU) Health Certificate for Fishery Products. With expanding world trade, ongoing international harmonization initiatives (such as the Codex Committee on Food Import and Export Inspection and Certification Systems, and WHO Certification Scheme on the Quality of Pharmaceutical Products), and developing international agreements, pressures on FDA to issue more certificates for-U.S. products are escalating.

Source: Compliance Policy Guidelines, Guide 7150.01, Chapter 50—General Policy, Form FDA 2678a(9/88) by Food and Drug Administration, Office of Enforcement, Division of Compliance Policy, Associate Commissioner for Regulatory Affairs.

POLICY

FDA's long term goal is to work towards the reduction or elimination of export certificates by finding other means to assure other countries of the acceptability of FDA regulated products. However, the agency recognizes the current importance of providing export certificates. For commodities regulated by FDA under authority of the Federal Food, Drug, and Cosmetic Act, or other acts FDA administers, FDA is the U.S. agency with regulatory oversight of the certification process. Therefore, the agency intends to provide for this service (either itself or by third parties under FDA oversight) with the anticipation of achieving full cost recovery by charging the requestor a fee based on the actual expenses incurred.

GUIDANCE

Each center may establish its own procedure for responding to requests for a "Certificate for Export" or similar requests. However, procedures implemented should place the burden and responsibility on the Certificate requestor to provide information that will allow FDA to issue a Certificate for Export. The following guidance has been developed to improve agency uniformity and consistency in providing export certifications for FDA regulated commodities:

1. The document provided should be entitled, "Certificate for Export," unless it is required to bear a different name.
2. It should be issued by the appropriate center compliance director, district director, or his/her designee.
3. If authentication of the certificate is required, the certificate may be certified under seal of the Department of Health and Human Services in accordance with 21 CFR 5.22, or notarized.
4. The individual representing the firm and submitting an export certificate request to FDA should sign a statement acknowledging awareness that he or she is subject to the provisions of Title 18, Section 1001 of the United States Code (U.S.C.). This statutory provision makes it a criminal offense to knowingly and willfully make a false or fraudulent statement, or make or use a false document, in any matter within the jurisdiction of a department or agency of the United States.

The provision also makes it a criminal offense to knowingly and willfully falsify, conceal, or cover up by any trick, scheme, or device a material fact in any matter within the jurisdiction of a department or agency of the United States.

5. The document should contain:

- a. A factual statement that the specific article(s) identified is subject to FDA jurisdiction;
- b. A statement indicating the compliance status of the system by which the commodity is required to be manufactured (may also indicate that the agency does not certify compliance with our laws for specific lots of product);
- c. For an article requiring pre-market approval (e.g., new drugs, new animal drugs, licensed biologics), or for an article subject to certification (e.g., insulin, colors), the statement should cover the article's premarket clearance status;
- d. For an electronic product subject to FDA performance standards (e.g., laser surgical devices), the statement should cover the model's compliance with the applicable standard;
- e. For an article (e.g., most foods and cosmetics) not subject to premarket clearance, a statement that named commodities are freely marketed in the United States or are eligible for export under 801(e) (and section 412 for infant formulas) if they meet certain specified requirements.

The requestor should be notified that the issuance of a "Certificate for Export" will not preclude regulatory action by FDA against products that are covered by such a certificate, if warranted. Additionally, the requestor should be informed that a "Certificate for Export" or similar statement issued by FDA is for export purposes only and may not be used for domestic advertising.

Regulatory Guidance

FDA intends to pursue regulatory action, including criminal prosecutions, against anyone responsible for causing the submission of false or misleading information, substitution of a product under a "Certificate for Export", counterfeiting or altering a certificate, or the misuse of a certificate.

Attachments:

General Model Certificate for Export
EU Export Health Certificate for Fishery Products
WHO Certificate for Quality of a Pharmaceutical Product

Issued: 10/01/80
Revised: 06/01/89
Revised: 8/15/94

Model Certificate for Export

The U.S. Food and Drug Administration certifies for [COUNTRY] the following information concerning the product listed below manufactured or distributed by [NAME OF COMPANY], [ADDRESS]:

NAME OF PRODUCT (GENERIC NAME IF APPLICABLE)
CENTRAL FILE NUMBER (CFN) (IF UNIQUE IDENTIFIER IS REQUIRED)
PREMARKET APPROVAL IDENTIFIER (IF APPLICABLE, I.E., NDA, NADA,
PMA NUMBER, 510(k) Number)

The product (and the plant which produces it) described above are subject to the jurisdiction of the Food and Drug Administration.

It is certified that the above listed product may be freely marketed in, or may otherwise be exported, from the United States of America at this time.

The manufacturing plant in which the products are produced is subject to periodic inspections, and the last such inspection showed that the plant, at that time, appeared to be in compliance with current Good Manufacturing Practice (GMP) required by the Federal Food, Drug, and Cosmetic Act.

Signature
Title
Food and Drug Administration

County of _____
State of _____

Subscribed and sworn to before me this _____ day of _____.

APPENDIX 2 - EC EXPORT HEALTH CERTIFICATE

CERTIFICATE NO. _____

HEALTH CERTIFICATE

Covering fishery products for import into the European Community.

Country of dispatch: _____
Competent authority (1): _____
Inspection body (1): _____
Reference number of health certificate: _____

1. Details identifying the fishery products

Description:

- Species (scientific name): _____
- State (2) or type of processing: _____
Type of packaging: _____
Number of packaging: _____
Net Weight: _____
Temperature required during storage and transport: _____

2. Provenance of the fishery products

Address(es) and number(s) of preparation or processing establishment(s) authorized for exports by the competent authority: _____

3. Destination of the fishery products

The fishery products are to be dispatched from: _____
_____ (Place of dispatch)
to: _____
(Country and place of destination)
by the following means of transport: _____

Name and address of consignor: _____

Name of consignee and address at place of destination: _____

Signature: _____ Date: _____

4. Health attestation

The undersigned official inspector hereby certifies that:

1. The fishery products above have been handled, prepared or processed, identified, stored and transported under conditions at least equivalent to those laid down in Council Directives 91/493/EC of 22 July 1991 laying down the health conditions for the production and the placing on the market of fishery products.

2. In addition, in the case of frozen or processed bivalve mollusks the latter have been gathered in production areas subject to conditions at least equivalent to those laid down in Council Directive 91/492/EC of 15 July 1991 laying down the health conditions for the production and the placing on the market of live bivalve mollusks.

Done at _____ on _____
(Place) (Date)

Signature of Official Inspector

Name in capitals, capacity and
qualifications

UNITED STATES FOOD AND DRUG ADMINISTRATION

SAMPLE
FD-361 (Rev. 12-88)

Certificate No.
(Conforms to WHO format)

Exporting Country: USA

Importing Country:

CERTIFICATE OF A PHARMACEUTICAL PRODUCT

Proprietary Name (if applicable) and dosage form:

Active Ingredient(s) and amount(s) per unit dose: SEE ATTACHED APPROVED LABELING

1. Is this product licensed to be placed on the market for use in the exporting country? If yes, complete box A; if no, complete box B

A	B
Product license holder:	Applicant for certificate:
Status of license holder: APPROVED	Status of Applicant:
Number of product license and date of issuance:	Why is authorization lacking? not not under required requested consideration refused
Is an approved technical summary appended? NO	
Is the attached product information complete and consonant with the license? YES	
Applicant for certificate if different from the license holder:	

2. Does the certifying authority arrange for periodic inspection of the manufacturing plant in which the dosage form is produced? **Yes**

Periodicity of routine inspection (years): **Every 2 years per U.S.A. regulations**

Has the manufacture of this type of dosage form been inspected? **Yes**

Do the facilities and operations conform to GMP as recommended by the World Health Organization? **Yes, at time of inspection**

3. Does the information submitted by the applicant satisfy the authority on all aspects of the manufacturer of the product undertaken by another party?
YES NO If no, explain:

Address of certifying authority: U.S. Food and Drug Administration

7520 Standish Place
Rockville, MD 20855, USA
Telephone: (301) 594-0063

Deputy Director, Division of
Drug Labeling Compliance
Center for Drug Evaluation
and Research

State of Maryland Subscribed and sworn before me
County of Montgomery This _____ Day of _____, 1994.

THIS CERTIFICATE EXPIRES TWELVE MONTHS FROM THE DATE NOTARIZED

Notary Public

Enhancement of Global Product Distribution

After one has read the previous chapter, it may be helpful to consider the additional effects of the FDA Export Reform and Enhancement Act of 1996 in some special areas of importation and exportation that have come to light since the effectuation of the Act on April 26, 1996.

With respect to these, it is still helpful to look at the materials from the FDA Compliance Guides that are attached for study review at the end of this chapter.

Among important changes in the statute, the new Section 801(d)(3) authorizes importation of drug “component(s)” or “component part or accessory device,” food additive, color additive, or dietary supplement that is “intended to be incorporated by the initial owner or consignee (importer), into a drug, biological product, device, food, food additive, color additive, or dietary supplement that will be exported as permitted under this statute.”

This might include an unapproved drug imported into the United States to be incorporated in a transdermal delivery system here and then re-exported back to the country of origin (which approves its use) for sale there.

Certain pre-conditions to be met include informing the FDA of the intentions, destruction of any overage not re-exported, and records to be kept that will account for materials imported, processed, re-exported.

This authority section excluded specifically blood, components, source plasma, source leukocytes, or tissue (Section 801(d)(4)).

Section 801(e)(4) provides for a means to request from the FDA, and acquire, a certificate that a drug, animal drug, or device may legally be exported under the statute. It permits the FDA to charge up to \$175 for each such certificate within 20 days from the time of request. An example of this certificate has been provided.

Section 801(f) can cause some degree of confusion involving the labeling of the drug being exported under the prior section of the statute. If the export target has “different or additional labeling requirements or conditions for use,” the exporter can label as per such exportee’s requirements of U.S. law. So, if the labeling for this exportee includes “conditions for use” that are not acceptable by the FDA, the labeling must clearly indicate that these stated conditions of use are not approved under the U.S. statute. Some compliance alternatives would seem to apply.

There seems some room to argue that including “unapproved conditions for use” may affect compliance with Section 505 of the FDCA, “new drug status.”

In fact, when we examine the extensive revision of Section 802, the ability to manufacture, in the United States, non-FDA-approved drugs for exportation seems encouraged.

So, the new Section 802 establishes a basis under which unapproved new drugs, unlicensed biologicals, devices noncompliant with a performance standard, or lacking a PMA or an IDE, as well as devices banned by the FDA, may be exported. Thus, Section 802(b)(1) provides that “a drug or device . . . may be exported to any country,” (so long as it’s authorized for marketing in at least one of the 802(b)(1) countries, it may be exported to any country in the world).

If the drug or device complies with the laws of that country “and has valid marketing authorization by the appropriate authority (1) in Australia, Canada, Israel, Japan, New Zealand, Switzerland or South Africa; or (ii) In the EU . . . if authorized for general marketing in the European Economic Area.”

Note that the new law eliminates the requirement that the exporter have an active IND and be pursuing the FDA approval process. It is business oriented and also renders unnecessary the requirement that FDA affirmatively OK the export and the somewhat convoluted procedures calculated to guard against transshipment to countries other than listed in the former Section 802.

The new statute potentially expands the list of countries eligible (Section 802(b)(1)(B)) making eligible new countries that have a capacity to regulate imported products subject to the FDCA.

Exporters of drugs and/or devices under the new law provide a simple notice to the FDA identifying the export when it first begins. Of course, they will expect recourse to the records kept of the exportation(s).

For drugs approved in an unlisted country, exportation may be accomplished under Section 802(b)(2) if the drug is legally compliant in its destination country and may be legally marketed there.

It is foreseeable that drugs not approved in the U.S. or the named countries might be granted exportation privilege under special process of petition. For details, see Section 802(b)(2).

At present, thanks to new Section 802(C), drugs or devices intended for export so they can undergo investigational use in any of the countries listed may be exported in accordance with the laws of that country and enjoy exemption from regulation as an investigational drug or device under the U.S. statute. Thus, this has much simplified a former circular process that was time consuming for getting drugs in the hands of foreign clinicians doing an investigational study.

Many of our readers are concerned with exporting drugs or devices for additional manufacturing overseas. Under Section 802(d), such products “intended for formulation, filling, packaging, labeling, or further processing in anticipation of market authorization” in any of the countries listed below may be exported for use in accordance with the laws of the country (minus notice to the FDA).

The new law under Section 802(e) also eases the exportation of drugs or devices used for diseases that are unlikely to be found in the United States of America. But the FDA must make a prior determination of a reasonable degree of safety and favorable risk-benefit ratio.

Good Manufacturing Practices must be adhered to, as was required by the past law, for drugs and devices intended for exportation.

Under Section 802(f), exportation can be denied if labeling and label do not conform with requirements of country of destination, or do not measure or weigh in units there in use.

What of drugs that are on their face so dangerous because of possibility of reimportation or would similarly represent an imminent hazard in the country of destination? As you might expect, the FDA can prohibit their exportation.

Under the new law, an important advantage is given to partially processed biologicals that was restricted from their use under the prior statute. At present they have similar status as drug intermediates in the export reform. But as in the case of the drug intermediates, the product must be manufactured, processed, packaged and held in conformity with the CGMPs, or meet international standards organization recognized by FDA and meet requirements of Section 801(e)(1).

Following study of this chapter, it might be helpful for staff review, to discuss specific guides provided by the FDA to their field staff and others, that are pertinent as Regulatory Action Guidance.

Model Certificate for Export

The U.S. Food and Drug Administration certifies for [COUNTRY] the following information concerning the product listed below manufactured or distributed by [NAME OF COMPANY], [ADDRESS]:

NAME OF PRODUCT (GENERIC NAME IF APPLICABLE)

CENTRAL FILE NUMBER (CFN) (IF UNIQUE IDENTIFIER IS REQUIRED)

PREMARKET APPROVAL IDENTIFIER (IF APPLICABLE, I.E., NDA, NADA, PMA NUMBER, 510(k) Number)

The product (and the plant which produces it) described above are subject to the jurisdiction of the Food and Drug Administration.

It is certified that the above listed product may be freely marketed in, or may otherwise be exported, from the United States of America at this time.

The manufacturing plant in which the products are produced is subject to periodic inspections, and the last such inspection showed that the plant, at that time, appeared to be in compliance with current Good Manufacturing Practice (GMP) required by the Federal Food, Drug, and Cosmetic Act.

Signature

Title

Food and Drug Administration

Country of _____
State of _____

Subscribed and sworn to before me this _____ day of _____.

Figure 24.1

SUB CHAPTER 110 EXPORTS/IMPORTS

Sec. 110.100 Certification for Exports (CPG 7150.01)

BACKGROUND:

Firms exporting products from the U.S. are often asked by foreign customers or foreign governments to supply a certification relating to products subject to the Federal Food, Drug, and Cosmetic Act and other acts FDA administers. Certification is the process by which a formal or official attestation is made concerning the regulatory status of a product, or the system by which a commodity is manufactured. Requests for certification have variously asked for verification that the products being exported: (1) are freely marketed

UNITED STATES FOOD AND DRUG ADMINISTRATION

Certificate No.
(Conforms to WHO format)

Exporting Country: USA
Importing Country:

CERTIFICATE OF A PHARMACEUTICAL PRODUCT

Proprietary Name (if applicable) and dosage form:

Active Ingredient(s) and amount(s) per unit dose: SEE ATTACHED APPROVED LABELING

1. Is this product licensed to be placed on the market for use in the exporting country? If yes, complete box A; if no, complete B

A	B
Product license holder:	Application for Certificate:
Status of License Holder: APPROVED	Status of Applicant:
Number of product license and date of issuance:	Why is authorization lacking? not required not requested consideration refused
Is an approved technical summary appended? NO	
Is the attached product information complete and consistent with the license? YES	
Applicant for certificate if different from the license holder:	

2. Does the certifying authority arrange for periodic inspection of the manufacturing plant in which the dosage form is produced: Yes
Periodicity of routine inspection (years): Every 2 years per U.S.A. regulations
Has the manufacture of this type of dosage form been inspected: Yes
Do the facilities and operations conform to GMP as recommended by the World Health Organization: Yes, at time of inspection
3. Does the information submitted by the applicant satisfy the authority on all aspects of the manufacturer of the product undertaken by another party?

Address of certifying authority: U.S. Food and Drug Administration

7520 Standish Place
Rockville, MD 20855, USA
Telephone: (301) 594-0063

Deputy Director, Division of
Drug Labeling Compliance
Center for Drug Evaluation and Research

State of Maryland Subscribed and sworn before me
County of Montgomery This _____ Day of _____, 1994.

THIS CERTIFICATE EXPIRES TWELVE MONTHS FROM THE DATE NOTARIZED

Notary Public

Figure 24.2

in the U.S.; (2) are in compliance with U.S. laws and regulations; (3) are in compliance with the importing country's requirements; (4) meet certain national or international standards, such as quality standards; or (5) do not contain specific contaminants. This certification process may include issuance of a certificate to accompany the exported product.

FDA has historically issued a number of different types of certificates, e.g. Certificates of Free Sale, Certificates for Export, Certificates to Foreign Governments, and most recently the European Union (EU) Health Certificate for Fishery Products. With expanding world trade, ongoing international harmonization initiatives (such as the Codex Committee on Food Import and Export Inspection and Certification Systems, and WHO Certification Scheme on the Quality of Pharmaceutical Products), and developing international agreements, pressures on FDA to issue more certificates for U.S. products are escalating.

POLICY:

FDA's long term goal is to work towards the reduction or elimination of export certificates by finding other means to assure other countries of the acceptability of FDA regulated products. However, the agency recognizes the current importance of providing export certificates. For commodities regulated by FDA under authority of the Federal Food, Drug, and Cosmetic Act, or other acts FDA administers, FDA is the U.S. agency with regulatory oversight of the certification process. Therefore, the agency intends to provide for this service (either itself or by third parties under FDA oversight) with the anticipation of achieving full cost recovery by charging the requestor a fee based on the actual expenses incurred.

GUIDANCE:

Each center may establish its own procedure for responding to requests for a "Certificate for Export" or similar requests. However, procedures implemented should place the burden and responsibility on the Certificate requestor to provide information that will allow FDA to issue a Certificate for Export. The following guidance has been developed to improve agency uniformity and consistency in providing export certifications for FDA regulated commodities:

1. The document provided should be entitled, "Certificate for Export," unless it is required to bear a different name.
2. It should be issued by the appropriate center compliance director, district director, or his/her designee.
3. If authentication of the certificate is required, the certificate may be certified under seal of the Department of Health and Human Services in accordance with 21 CFR 5.22, or notarized.
4. The individual representing the firm and submitting an export certificate request to FDA should sign a statement acknowledging awareness that he or she is subject to the provisions of Title 18, Section 1001 of the United States Code (U.S.C.). This statutory provision makes it a criminal offense to knowingly and

willfully make a false or fraudulent statement, or make or use a false document, in any matter within the jurisdiction of a department or agency of the United States. The provision also makes it a criminal offense to knowingly and willfully falsify, conceal, or cover up by any trick, scheme, or device a material fact in any matter within the jurisdiction of a department or agency of the United States.

5. The document should contain:
 - A. A factual statement that the specific article(s) identified is subject to FDA jurisdiction;
 - B. A statement indicating the compliance status of the system by which the commodity is required to be manufactured (may also indicate that the agency does not certify compliance with our laws for specific lots of product);
 - C. For an article requiring pre-market approval (e.g., new drugs, new animal drugs, licensed biologics), or for an article subject to certification (e.g., insulin, colors), the statement should cover the article's premarket clearance status;
 - D. For an electronic product subject to FDA performance standards (e.g., laser surgical devices), the statement should cover the model's compliance with the applicable standard;
 - E. For an article (e.g., most foods and cosmetics) not subject to premarket clearance, a statement that named commodities are freely marketed in the United States or are eligible for export under 801(e) (and section 412 for infant formulas) if they meet certain specified requirements.

The requestor should be notified that the issuance of a "Certificate for Export" will not preclude regulatory action by FDA against products that are covered by such a certificate, if warranted. Additionally, the requestor should be informed that a "Certificate for Export" or similar statement issued by FDA is for export purposes only and may not be used for domestic advertising.

REGULATORY GUIDANCE:

FDA intends to pursue regulatory action, including criminal prosecutions, against anyone responsible for causing the submission of false or misleading information, substitution of a product under a "Certificate for Export", counterfeiting or altering a certificate, or the misuse of a certificate.

Attachments:

General Model Certificate for Export
EU Export Health Certificate for Fishery Products
WHO Certificate for Quality of a Pharmaceutical Product

Issued: 10/1/80

Revised: 6/1/89, 8/15/94

Sec. 110.200 Export of FDA Regulated Products from U. S. Foreign Trade Zones (CPG 7150.11)

BACKGROUND:

From time to time industry inquires whether regulated products can be manufactured in a Foreign Trade Zone (Free Trade Zone) and exported without meeting the requirements of the laws and regulations administered by the Food and Drug Administration.

Foreign Trade Zones are provided in the United States by the U. S. Customs Service for the trade to hold or otherwise manipulate goods for an unlimited period of time awaiting a favorable market in the U. S. or nearby countries without being subject to customs entry, payment of duty, tax, or bond. The location of an establishment in a Foreign Trade Zone has absolutely no bearing on the jurisdiction of the Food and Drug Administration or the applicability of the laws it administers.

POLICY:

For the purposes of the laws enforced by the FDA, Foreign Trade Zones are part of the United States and the movement of regulated products into or out of such zones, including export, constitutes interstate commerce. Therefore, regulated products in Foreign Trade Zones must comply with those laws that come within the purview of FDA.

** Reference: See United States v. Yaron Laboratories, Inc., 365 F. Supp. 917 (N.D. Calif., 1972.)**

** Material between asterisks is new or revised **

Issued: 1/5/79

Revised: 10/1/80, 8/31/89

Sec. 110.500 Food and Drug Guaranty—Imports (CPG 7153.10)

BACKGROUND:

A district compliance officer has inquired if a domestic distributor can take advantage of the immunity offered by 21 USC 333(c)(2) by obtaining from a foreign manufacturer, or his resident agent, a continuing guaranty.

POLICY:

21 USC 333(c)(2) provides immunity only if the person against whom action is contemplated establishes “a guaranty or undertaking signed by and containing the name and address of the persons residing in the U.S. from whom he received in good faith the article . . .”. It is thus apparent from the law itself that the guarantor must be a U.S. resident to comply with the act.

There seems to be no reason, however, that the domestic agent of the foreign manu-

facturer, if he resides in the U.S., could not provide such a guaranty to the distributor. The law does not require that the guaranty be given by the manufacturer, wholesaler, packer or any other person in the direct line of distribution. All that is required is that the signer of the guaranty be a resident of the U.S. and be the person from whom the distributor received the article.

21 USC 333(c)(3) also provides immunity in case of adulteration caused by the presence of an guaranty so specifies.

Issued: 10/1/80

Sec. 110.600 FDA Authority Over Products of Foreign Origin Located in Foreign Trade Zones, Bonded Warehouses or on Bonded Carriers (CPG 7150.14)

BACKGROUND:

On occasion, questions have been raised concerning FDA's authority over foreign origin products brought into the U.S. for which no entry has been filed or importation has not been made. These products are usually located in U.S. Foreign (Free) Trade Zones. However, they may also be found in bonded warehouses or in bonded vehicles.

As stated in CPG 7150.11 (See Sec. 110.200) "Export of FDA Regulated Products from U.S. Foreign Trade Zones", such zones are provided by the U.S. Customs Service as a means of avoiding payment of duty, tax, and bond if the goods are not intended for entry for consumption, to delay such payment until actual entry for consumption is made.

Products of foreign origin located in Foreign Trade Zones or in bonded warehouses are in the United States, are in interstate commerce and are therefore subject to the laws administered by FDA.

Products entered for transportation and exportation (in bond for transportation through the United States by a bonded carrier without appraisalment or the payment of duties) are also subject to the laws administered by FDA.

POLICY:

FDA has the authority to regulate products of foreign origin brought into the U.S. whether or not entry has been filed. The location of goods (truck, bonded warehouse, Foreign Trade Zones, etc.) does not affect FDA's authority over the goods.

Products not imported or offered for import:

Those products of foreign origin not offered for import but located within the legal boundaries of the U.S. are to be regulated under the domestic provisions of statutes.

Products imported or offered for import:

Those products (whether in Foreign Trade Zones, bonded warehouses, etc.) which have been offered for entry and those already imported but still in import status are regulated under the provisions of section 801 of the FD&C Act or 360(a) of the RCHS Act.

Issued: 4/1/82

Revised: 8/31/89

**Sec. 110.700 Seizures by the U.S. Customs Service of
Prohibited Articles of Foreign Origin Not
Intended for Entry into the United States
(CPG 7153.08)**

BACKGROUND:

19 CFR 18.21(b) states: "Narcotics and other articles prohibited admission into commerce of the United States shall not be entered for transportation and exportation and any such merchandise offered for entry for that purpose shall be seized, except that exportation or transportation and exportation may be permitted upon written authority from the proper governmental agency and on compliance with the regulations of such agency."

* For example, * a shipment of amygdalin was entered for transportation and exportation and was seized by the U. S. Customs Service as a prohibited article. The importer was notified that consideration for release for export of the article must be obtained from the Food and Drug Administration. The importer wrote us requesting such release for export. In response, we informed the importer that we fully supported the U. S. Customs Service in their action and that we would not authorize the exportation of the article, since the importation, exportation, or other shipment in interstate commerce of amygdalin is prohibited by the Federal Food, Drug, and Cosmetic Act.

POLICY:

FDA supports the use of seizure by the U.S. Customs Service under authority of 19 CFR 18.21 (b) of articles regulated by FDA, which are offered under a Transportation and Exportation Entry (T & E), if certain conditions are met. Such conditions may be: the article poses a hazard to health, consists of gross filth, or represents a gross consumer fraud * For we have reason to believe the article may be offered for entry into the U.S. at a later date or that its routing might be deviated during transit. *

If Customs has seized and the importer requests release of the article for export; if Customs inquires whether they should seize; or if we believe Customs should seize under the authority of 19 CFR 18.21 (b) articles regulated by FDA offered under a Transportation and Exportation Entry (T & E), the facts should be sent to the appropriate * Center * for action and/or consideration.

* Material between asterisks is new or revised *

Issued: 11/26/76

Revised: 10/1/80, 8/31/89

Sec. 110.800 Imports, Post Detention Sampling (CPG 7150.04)

BACKGROUND:

* Importers sometimes request from FDA, rather than Customs, permission to take samples from detained lots for the purpose of analysis, or other examination, usually to explore the possibility of reconditioning or contest. Frequently the imported lot may be physically in possession of the importer and held under redelivery bond or in Customs custody pending final disposition. *

POLICY:

* The Food and Drug Administration has no objection to an importer taking reasonable samples for appropriate analysis or other examination from detained shipments. Whether the goods are in Customs custody or in physical possession of the importer under redelivery bond, the importer must assume responsibility for obtaining permission from Customs and complying with any instructions from that agency. The importer must take such steps as may be necessary to account to Customs for whatever amount is missing if he is called upon to redeliver the detained lot to Customs custody for destruction or exportation. *

* Material between asterisks is new or revised *

Issued: 3/15/77

Revised: 10/1/80, 8/31/89

Sec. 110.900 Imported Products—Lack of English Labeling (CPG 7150.15)

BACKGROUND:

Violative imported products should preferably be handled at the port of entry. However, all imported products entered into the United States are not sampled or examined. In fact, most imported articles subject to the agency's jurisdiction are given a "May Proceed Notice" upon entry and are not examined prior to entering domestic commerce. Although the agency attempts to sample or examine as many potentially violative products as possible, it is inevitable that some violative foreign products enter into United States commerce.

On occasion, violative imported products that are labeled solely in a foreign language [violation of 21 CFR 101.15(c)(1) for foods, 21 CFR 201.15(c)(1) for drugs, 21

CFR 501.15(c)(1) for animal drugs, 21 CFR 701.2(b)(1) for cosmetics, and 21 CFR 801.15(c)(1) for medical devices] are able to enter into United States commerce without being detained when they are in import status. At some point later, these foreign labeled products may be brought to the agency's attention by a complaint. When this occurs, the most desirable solution is voluntary correction (e.g., relabeling or destruction). Failing voluntary correction, the action of choice is seizure of the misbranded lot.

NOTE: These sections contain an exemption which allows for labeling in the predominant language other than English, in the Commonwealth of Puerto Rico or in a U.S. territory.

REGULATORY ACTION GUIDANCE:

Violative imported products should be dealt with at the port of entry whenever possible. In the few instances where products labeled solely in a foreign language gain entry without examination, district offices are authorized to refer for direct reference seizure to the * Office of Chief Counsel (GCF-1) * through the Division of Compliance Management and Operations (HFC-210), seizable size lots (\$1,000 or more) of foods, drugs, animal feeds or drugs, cosmetics and medical devices, which are labeled solely in a foreign language when the owner or other party controlling the lot refuses to voluntarily correct the violation. In instances where this occurs, the district should take appropriate steps to assure that future import shipments either comply with our laws or are detained at the port of entry. This may entail intensive coverage of FDA regulated commodities imported by that firm.

For lots valued under \$1,000 attempt to obtain state or local condemnation.

* Material between asterisks is new or revised *

Issued: 3/1/84

Revised: 8/31/89, 3/95, 8/96

SUB CHAPTER 120 FRAUD

Sec. 120.100 Fraud, Untrue Statements of Material Facts, Bribery, and Illegal Gratuities (CPG 7150.09)

BACKGROUND:

The House Subcommittee on Oversight and Investigations began an investigation of wrongful acts involving some manufacturers of generic drugs and some employees of the Food and Drug Administration (FDA) during July 1988. As a result of those investigations and investigations conducted by FDA, four FDA employees were found to have accepted illegal gratuities from generic drug companies, and to date, eleven generic drug companies were found to have falsified data submitted in premarket applications to FDA.

In FDA's investigations, which began as inquiries into illegal gratuities and questionable data submissions, the agency discovered broad patterns and practices of fraud in

the applicants' abbreviated new drug applications. The discovery of this extensive pattern of fraudulent data submissions prompted FDA to develop a program (1) to ensure validity of data submissions called into question by the agency's discovery of wrongful acts such as fraud, untrue statements of material fact, bribery, and illegal gratuities and (2) to withdraw approval of, or refuse to approve, applications containing fraudulent data. This guide sets forth the agency's general approach to applications that have been called into question by such wrongful acts and applications found to contain fraudulent data.

TERMINOLOGY:

The terms "applicant" and "application" are used broadly in this policy statement. References to the "applicant" include any person within the meaning of section 201 (e) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 321 (e)) who submits to FDA data or other information to influence or support an agency decision regarding approval to market an FDA-regulated product. Actions by an applicant's employees or agents are considered actions by the applicant.

References to the "application" include any application, petition, amendment, supplement, or other submission made by an applicant to an agency review process in support of the approval or marketing of a regulated product. These review processes include, but are not limited to, new drug and new animal drug approvals, biological product and establishment licensing, premarket notification, classification, and premarket approval of medical devices, food additive petitions, and color additive petitions. References to data in an application include all data and other information submitted in or in relation to, or incorporated by reference in, the application.

POLICY:

Validity Assessment

Actions on the part of an applicant to subvert the integrity of an FDA review process through acts such as submitting fraudulent applications, making untrue statements of material facts, or giving or promising bribes or illegal gratuities may call into question the integrity of some or all of the applicant's submissions to the agency.

Sec. 405.200 Export of Uncertified Antibiotics (CPG 7122.02)

BACKGROUND:

Questions have arisen as to whether antibiotics which have not been certified in accordance with Section 507 of the Act may be exported. In addition, there is also some disagreement as to what antibiotic drugs are subject to Section 505 instead of Section 507 and what the conditions for export are for these drugs.

POLICY:

A certifiable antibiotic drug subject to Section 507 of the Act is not subject to any provision of Section 505 and can be exported even if the lot is uncertified if it is in conformance with Section 801(d) of the Act. This is elaborated upon in 21 CFR 433.25.

A new antibiotic drug, exempted under Section 507(e) is a new drug subject to Section 505. As such, it may not be introduced or delivered for introduction into interstate commerce including export in the absence of an approved new drug application.

When a new drug application is approved for a new antibiotic, it is regarded as a certifiable antibiotic subject to Sections 507 and 502(i) and may be exported provided that it is in conformance with Section 801(d) of the Act.

NOTE: Legislation presently pending before both houses of Congress would discontinue the disparate requirements for the export of antibiotic and non-antibiotic drugs. Export of unapproved antibiotic drugs will be more restrictive *if this legislation is passed*.

Issued: 10/1/80

Sec. 405.210 Returned Antibiotics Exported Under 801(d) of the Act (CPG 7122.03)

BACKGROUND:

From time-to-time situations have occurred where uncertified antibiotics exported under 801(d) of the Act, have been returned to the United States for a variety of reasons such as being in surplus or failure to meet the foreign consignee's specifications, container or product damage, etc. Returned pharmaceuticals, including uncertified finished antibiotics are considered to be imports and, as such, are held by U.S. Customs for FDA examination. Generally, due to their U.S. origin, returned pharmaceutical have been allowed entry by the FDA without examination. However, a problem exists regarding uncertified finished antibiotics (bulks and dosage forms) in that since they are not from a certified batch they must be refused entry except under the conditions set forth in 801(b) of the Act.

POLICY:

Uncertified antibiotics exported from the U.S. and subsequently returned are considered to be imports by the FDA. If such returns would require certification for domestic distribution, they must be detained because they are misbranded under 502(i) of the Act due to their uncertified status. They may be released only to the original U.S. exporter for reconditioning under Section 801(b) of the Act if we are provided with an acceptable written plan (FD-766, Application to Relabel or Perform other Action) to bring the uncertified antibiotics into compliance. In general, uncertified antibiotics may be brought into compliance by either:

1. Conversion into a chemical entity of possible use in the production of another antibiotic product or chemical precursor, or

2. Reworking to resolve the problem that caused its return. In this instance the product may be released for export under 801(d), or, if subsequently certified, released unconditionally.

In lieu of the above options the product may be converted into a product or substance not subject to the Act or destroyed in a manner acceptable to FDA and released from import status.

Complete records must be kept which show the receipt, examination, handling, storage, and ultimate disposition of the material as required by the CGMP regulations (21 CFR 211).

Issued: 7/1/81

Appendix A

Food and Drug Modernization Act of 1997—in Pertinent Part

An Act

To amend the Federal Food, Drug and Cosmetic Act and the Public Health Service Act to improve the regulation of food, drugs, devices, and biological products, and for other purposes. *Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,*

SECTION 1. SHORT TITLE; REFERENCES; TABLE OF CONTENTS.

(a) SHORT TITLE—This Act may be cited as the ‘Food and Drug Administration Modernization Act of 1997’.

(b) REFERENCES—Except as otherwise specified, whenever in this Act an amendment or repeal is expressed in terms of an amendment to or a repeal of a section or other provision, the reference shall be considered to be made to that section or other provision of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 301 et seq.).

(c) TABLE OF CONTENTS—The table of contents for this Act is as follows:

TITLE I—IMPROVING REGULATION OF DRUGS SUBTITLE A—FEES RELATING TO DRUGS

Sec. 101. Findings.

Sec. 102. Definitions.

Sec. 103. Authority to assess and use drug fees.

- Sec. 104. Annual reports.
- Sec. 105. Savings.
- Sec. 106. Effective date.
- Sec. 107. Termination of effectiveness.

SUBTITLE B—OTHER IMPROVEMENTS

- Sec. 111. Pediatric studies of drugs.
- Sec. 112. Expediting study and approval of fast track drugs.
- Sec. 113. Information program on clinical trials for serious or life-threatening diseases.
- Sec. 114. Health care economic information.
- Sec. 115. Clinical investigations.
- Sec. 116. Manufacturing changes for drugs.
- Sec. 117. Streamlining clinical research on drugs.
- Sec. 118. Data requirements for drugs and biologics.
- Sec. 119. Content and review of applications.
- Sec. 120. Scientific advisory panels.
- Sec. 121. Positron emission tomography.
- Sec. 122. Requirements for radiopharmaceuticals.
- Sec. 123. Modernization of regulation.
- Sec. 124. Pilot and small scale manufacture.
- Sec. 125. Insulin and antibiotics.
- Sec. 126. Elimination of certain labeling requirements.
- Sec. 127. Application of Federal law to practice of pharmacy compounding.
- Sec. 128. Reauthorization of clinical pharmacology program.
- Sec. 129. Regulations for sunscreen products.
- Sec. 130. Reports of postmarketing approval studies.
- Sec. 131. Notification of discontinuance of a life saving product.

TITLE II—IMPROVING REGULATION OF DEVICES

- Sec. 201. Investigational device exemptions.
- Sec. 202. Special review for certain devices.
- Sec. 203. Expanding humanitarian use of devices.
- Sec. 204. Device standards.
- Sec. 205. Scope of review; collaborative determinations of device data requirements.
- Sec. 206. Premarket notification.
- Sec. 207. Evaluation of automatic class III designation.
- Sec. 208. Classification panels.
- Sec. 209. Certainty of review timeframes; collaborative review process.
- Sec. 210. Accreditation of persons for review of premarket notification reports.
- Sec. 211. Device tracking.
- Sec. 212. Postmarket surveillance.
- Sec. 213. Reports.
- Sec. 214. Practice of medicine.
- Sec. 215. Noninvasive blood glucose meter.

- Sec. 216. Use of data relating to premarket approval; product development protocol.
- Sec. 217. Clarification of the number of required clinical investigations for approval.

TITLE III—IMPROVING REGULATION OF FOOD

- Sec. 301. Flexibility for regulations regarding claims.
- Sec. 302. Petitions for claims.
- Sec. 303. Health claims for food products.
- Sec. 304. Nutrient content claims.
- Sec. 305. Referral statements.
- Sec. 306. Disclosure of irradiation.
- Sec. 307. Irradiation petition.
- Sec. 308. Glass and ceramic ware.
- Sec. 309. Food contact substances.

TITLE IV—GENERAL PROVISIONS

- Sec. 401. Dissemination of information on new uses.
- Sec. 402. Expanded access to investigational therapies and diagnostics.
- Sec. 403. Approval of supplemental applications for approved products.
- Sec. 404. Dispute resolution.
- Sec. 405. Informal agency statements.
- Sec. 406. Food and Drug Administration mission and annual report.
- Sec. 407. Information system.
- Sec. 408. Education and training.
- Sec. 409. Centers for education and research on therapeutics.
- Sec. 410. Mutual recognition agreements and global harmonization.
- Sec. 411. Environmental impact review.
- Sec. 412. National uniformity for nonprescription drugs and cosmetics.
- Sec. 413. Food and Drug Administration study of mercury compounds in drugs and food.
- Sec. 414. Interagency collaboration.
- Sec. 415. Contracts for expert review.
- Sec. 416. Product classification.
- Sec. 417. Registration of foreign establishments.
- Sec. 418. Clarification of seizure authority.
- Sec. 419. Interstate commerce.
- Sec. 420. Safety report disclaimers.
- Sec. 421. Labeling and advertising regarding compliance with statutory requirements.
- Sec. 422. Rule of construction.

TITLE V—EFFECTIVE DATE

- Sec. 501. Effective date.
- SEC. 2. DEFINITIONS.

In this Act, the terms ‘drug’, ‘device’, ‘food’, and ‘dietary supplement’ have the meaning given such terms in section 201 of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 321).

TITLE I—IMPROVING REGULATION OF DRUGS
SUBTITLE A—FEES RELATING TO DRUGS

SEC. 101. FINDINGS.

Congress finds that—

- (1) prompt approval of safe and effective new drugs and other therapies is critical to the improvement of the public health so that patients may enjoy the benefits provided by these therapies to treat and prevent illness and disease;
- (2) the public health will be served by making additional funds available for the purpose of augmenting the resources of the Food and Drug Administration that are devoted to the process for review of human drug applications;
- (3) the provisions added by the Prescription Drug User Fee Act of 1992 have been successful in substantially reducing review times for human drug applications and should be—
 - (A) reauthorized for an additional 5 years, with certain technical improvements; and
 - (B) carried out by the Food and Drug Administration with new commitments to implement more ambitious and comprehensive improvements in regulatory processes of the Food and Drug Administration; and
- (4) the fees authorized by amendments made in this subtitle will be dedicated toward expediting the drug development process and the review of human drug applications as set forth in the goals identified, for purposes of part 2 of subchapter C of chapter VII of the Federal Food, Drug and Cosmetic Act, in the letters from the Secretary of Health and Human Services to the chairman of the Committee on Commerce of the House of Representatives and the chairman of the Committee on Labor and Human Resources of the Senate, as set forth in the Congressional Record.

SEC. 102. DEFINITIONS.

Section 735 (21 U.S.C. 379g) is amended—

- (1) in the second sentence of paragraph (1)—
 - (A) by striking ‘Service Act, and’ and inserting ‘Service Act,’; and
 - (B) by striking ‘September 1, 1992.’ and inserting the following: ‘September 1, 1992, does not include an application for a licensure of a biological product for further manufacturing use only, and does not include an application or supplement submitted by a State or Federal Government entity for a drug that is not distributed commercially. Such term does include an application for licensure, as described in subparagraph (D), of a large volume biological product intended for single dose injection for intravenous use or infusion.’;
- (2) in the second sentence of paragraph (3)—
 - (A) by striking ‘Service Act, and’ and inserting ‘Service Act,’; and
 - (B) by striking ‘September 1, 1992.’ and inserting the following: ‘September 1, 1992, does not include a biological product that is licensed for further manufacturing use only, and does not include a drug that is not distributed

commercially and is the subject of an application or supplement submitted by a State or Federal Government entity. Such term does include a large volume biological product intended for single dose injection for intravenous use or infusion.’;

- (3) in paragraph (4), by striking ‘without’ and inserting ‘without substantial’;
- (4) by amending the first sentence of paragraph (5) to read as follows:
- (5) The term ‘prescription drug establishment’ means a foreign or domestic place of business which is at one general physical location consisting of one or more buildings all of which are within five miles of each other and at which one or more prescription drug products are manufactured in final dosage form.’;
- (5) in paragraph (7)(A)—
 - (A) by striking ‘employees under contract’ and all that follows through ‘Administration,’ the second time it occurs and inserting ‘contractors of the Food and Drug Administration,’; and
 - (B) by striking ‘and committees,’ and inserting ‘and committees and to contracts with such contractors,’;
- (6) in paragraph (8)—
 - (A) in subparagraph (A)—
 - (i) by striking ‘August of’ and inserting ‘April of’; and
 - (ii) by striking ‘August 1992’ and inserting ‘April 1997’; and
 - (B) in subparagraph (B)—
 - (i) by striking ‘section 254(d)’ and inserting ‘section 254(c)’;
 - (ii) by striking ‘1992’ and inserting ‘1997’; and
 - (iii) by striking ‘102d Congress, 2d Session’ and inserting ‘105th Congress, 1st Session’; and
- (7) by adding at the end of the following:
- ‘(9) The term ‘affiliate’ means a business entity that has a relationship with a second business entity if, directly or indirectly—
 - ‘(A) one business entity controls, or has the power to control, the other business entity; or
 - ‘(B) a third party controls, or has power to control, both of the business entities.’.

SEC. 103. AUTHORITY TO ASSESS AND USE DRUG FEES.

- (a) TYPES OF FEES- Section 736(a) (21 U.S.C. 379h(a)) is amended—
 - (1) by striking ‘Beginning in fiscal year 1993’ and inserting ‘Beginning in fiscal year 1998’;
 - (2) in paragraph (1)—
 - (A) by striking subparagraph (B) and inserting the following:
 - ‘(B) PAYMENT- The fee required by subparagraph (A) shall be due upon submission of the application or supplement.’;
 - (B) in subparagraph (D)—
 - (i) in the subparagraph heading, by striking ‘NOT ACCEPTED’ and inserting ‘REFUSED’;
 - (ii) by striking ‘50 percent’ and inserting ‘75 percent’;
 - (iii) by striking ‘subparagraph (B)(i)’ and inserting ‘subparagraph (B)’; and
 - (iv) by striking ‘not accepted’ and inserting ‘refused’; and

(C) by adding at the end the following:

‘(E) EXCEPTION FOR DESIGNATED ORPHAN DRUG OR INDICATION-A human drug application for a prescription drug product that has been designated as a drug for a rare disease or condition pursuant to section 526 shall not be subject to a fee under subparagraph (A), unless the human drug application includes an indication for other than a rare disease or condition. A supplement proposing to include a new indication for a rare disease or condition in a human drug application shall not be subject to a fee under subparagraph (A), if the drug has been designated pursuant to section 526 as a drug for a rare disease or condition with regard to the indication proposed in such supplement.

‘(F) EXCEPTION FOR SUPPLEMENTS FOR PEDIATRIC INDICATIONS-A supplement to a human drug application proposing to include a new indication for use in pediatric populations shall not be assessed a fee under subparagraph (A).

‘(G) REFUND OF FEE IF APPLICATION WITHDRAWN-If an application or supplement is withdrawn after the application or supplement was filed, the Secretary may refund the fee or a portion of the fee if no substantial work was performed on the application or supplement after the application or supplement was filed. The Secretary shall have the sole discretion to refund a fee or a portion of the fee under this subparagraph. A determination by the Secretary concerning a refund under this paragraph shall not be reviewable.’;

(3) by striking paragraph (2) and inserting the following:

‘(2) PRESCRIPTION DRUG ESTABLISHMENT FEE-

‘(A) IN GENERAL- Except as provided in subparagraph (B), each person that—

‘(i) is named as the applicant in a human drug application; and

‘(ii) after September 1, 1992, had pending before the Secretary a human drug application or supplement, shall be assessed an annual fee established in subsection (b) for each prescription drug establishment listed in its approved human drug application as an establishment that manufactures the prescription drug product named in the application. The annual establishment fee shall be assessed in each fiscal year in which the prescription drug product named in the application is assessed a fee under paragraph (3) unless the prescription drug establishment listed in the application does not engage in the manufacture of the prescription drug product during the fiscal year. The establishment fee shall be payable on or before January 31 of each year. Each such establishment shall be assessed only one fee per establishment, notwithstanding the number of prescription drug products manufactured at the establishment. In the event an establishment is listed in a human drug

application by more than one applicant, the establishment fee for the fiscal year shall be divided equally and assessed among the applicants whose prescription drug products are manufactured by the establishment during the fiscal year and assessed product fees under paragraph (3).

‘(B) EXCEPTION- If, during the fiscal year, an applicant initiates or causes to be initiated the manufacture of a prescription drug product at an establishment listed in its human drug application—

‘(i) that did not manufacture the product in the previous fiscal year; and

‘(ii) for which the full establishment fee has been assessed in the fiscal year at a time before manufacture of the prescription drug product was begun; the applicant will not be assessed a share of the establishment fee for the fiscal year in which the manufacture of the product began.’; and

(4) in paragraph (3)—

(A) in subparagraph (A)—

(i) in clause (i), by striking ‘is listed’ and inserting ‘has been submitted for listing’; and

(ii) by striking ‘Such fee shall be payable’ and all that follows through ‘section 510.’ and inserting the following: ‘Such fee shall be payable for the fiscal year in which the product is first submitted for listing under section 510, or is submitted for relisting under section 510 if the product has been withdrawn from listing and relisted. After such fee is paid for that fiscal year, such fee shall be payable on or before January 31 of each year. Such fee shall be paid only once for each product for a fiscal year in which the fee is payable.’; and

(B) in subparagraph (B), by striking ‘505(j).’ and inserting the following: ‘505(j), under an abbreviated application filed under section 507 (as in effect on the day before the date of enactment of the Food and Drug Administration Modernization Act of 1997), or under an abbreviated new drug application pursuant to regulations in effect prior to the implementation of the Drug Price Competition and Patent Term Restoration Act of 1984.’.

(b) FEE AMOUNTS- Section 736(b) (21 U.S.C. 379h(b)) is amended to read as follows:

‘(b) FEE AMOUNTS- Except as provided in subsections (c), (d), (f), and (g), the fees required under subsection (a) shall be determined and assessed as follows:

‘(1) APPLICATION AND SUPPLEMENT FEES-

‘(A) FULL FEES- The application fee under subsection (a)(1)(A)(i) shall be \$250, 704 in fiscal year 1998, \$256, 338 in each of fiscal years 1999 and 2000, \$267, 606 in fiscal year 2001, and \$258, 451 in fiscal year 2002.

‘(B) OTHER FEES- The fee under subsection (a)(1)(A)(ii) shall be \$125, 352 in fiscal year 1998, \$128, 169 in each of fiscal years 1999

and 2000, \$133, 803 in fiscal year 2001, and \$129, 226 in fiscal year 2002.

‘(2) TOTAL FEE REVENUES FOR ESTABLISHMENT FEES- The total fee revenues to be collected in establishment fees under subsection (a)(2) shall be \$35,600,000 in fiscal year 1998, \$36,400,000 in each of fiscal years 1999 and 2000, \$38,000,000 in fiscal year 2001, and \$36,700,000 in fiscal year 2002.

‘(3) TOTAL FEE REVENUES FOR PRODUCT FEES- The total fee revenues to be collected in product fees under subsection (a)(3) in a fiscal year shall be equal to the total fee revenues collected in establishment fees under subsection (a)(2) in that fiscal year.’.

(c) INCREASES AND ADJUSTMENTS- Section 736(c) (21 U.S.C. 379h (c)) is amended—

(1) in the subsection heading, by striking ‘INCREASES AND’;

(2) in paragraph (1)—

(A) by striking ‘(1) REVENUE’ and all that follows through ‘increased by the Secretary’ and inserting the following: ‘(1) INFLATION ADJUSTMENT- The fees and total fee revenues established in subsection (b) shall be adjusted by the Secretary’;

(B) in subparagraph (A), by striking ‘increase’ and inserting ‘change’;

(C) in subparagraph (B), by striking ‘increase’ and inserting ‘change’; and

(D) by adding at the end the following flush sentence: ‘The adjustment made each fiscal year by this subsection will be added on a compounded basis to the sum of all adjustments made each fiscal year after fiscal year 1997 under this subsection.’;

(3) in paragraph (2), by striking ‘October 1, 1992,’ and all that follows through ‘such schedule.’ and inserting the following: ‘September 30, 1997, adjust the establishment and product fees described in subsection (b) for the fiscal year in which the adjustment occurs so that the revenues collected from each of the categories of fees described in paragraphs (2) and (3) of subsection (b) shall be set to be equal to the revenues collected from the category of application and supplement fees described in paragraph (1) of subsection (b).’; and

(4) in paragraph (3), by striking ‘paragraph (2)’ and inserting ‘this subsection’.

(d) FEE WAIVER OR REDUCTION- Section 736(d) (21 U.S.C. 379h (d)) is amended—

(1) by redesignating paragraphs (1), (2), (3), and (4) as subparagraphs (A), (B), (C), and (D), respectively and indenting appropriately;

(2) by striking ‘The Secretary shall grant a’ and all that follows through ‘finds that—’ and inserting the following:

‘(1) IN GENERAL- The Secretary shall grant a waiver from or a reduction of one or more fees assessed under subsection (a) where the Secretary finds that—’;

(3) in subparagraph (C) (as so redesignated in paragraph (1)), by striking ‘, or’ and inserting a comma;

- (4) in subparagraph (D) (as so redesignated in paragraph (1)), by striking the period and inserting ‘, or’;
 - (5) by inserting after subparagraph (D) (as so redesignated in paragraph (1)) the following:
 - ‘(E) the applicant involved is a small business submitting its first human drug application to the Secretary for review.’; and
 - (6) by striking ‘In making the finding in paragraph (3),’ and all that follows through ‘standard costs.’ and inserting the following:
 - ‘(2) USE OF STANDARD COSTS- In making the finding in paragraph (1)(C), the Secretary may use standard costs.
 - ‘(3) RULES RELATING TO SMALL BUSINESSES—
 - ‘(A) DEFINITION- In paragraph (1)(E), the term ‘small business’ means an entity that has fewer than 500 employees, including employees of affiliates.
 - ‘(B) WAIVER OF APPLICATION FEE- The Secretary shall waive under paragraph (1)(E) the application fee for the first human drug application that a small business or its affiliate submits to the Secretary for review. After a small business or its affiliate is granted such a waiver, the small business or its affiliate shall pay—
 - ‘(i) application fees for all subsequent human drug applications submitted to the Secretary for review in the same manner as an entity that does not qualify as a small business; and
 - ‘(ii) all supplement fees for all supplements to human drug applications submitted to the Secretary for review in the same manner as an entity that does not qualify as a small business.’
- (e) ASSESSMENT OF FEES- Section 736(f)(1) (21 U.S.C. 379h(f)(1)) is amended—
- (1) by striking ‘fiscal year 1993’ and inserting ‘fiscal year 1997’; and
 - (2) by striking ‘fiscal year 1992’ and inserting ‘fiscal year 1997 (excluding the amount of fees appropriated for such fiscal year)’.
- (f) CREDITING AND AVAILABILITY OF FEES- Section 736(g) (21 U.S.C. 379h (g)) is amended—
- (1) in paragraph (1), by adding at the end the following: ‘Such sums as may be necessary may be transferred from the Food and Drug Administration salaries and expenses appropriation account without fiscal year limitation to such appropriation account for salaries and expenses with such fiscal year limitation. The sums transferred shall be available solely for the process for the review of human drug applications.’;
 - (2) in paragraph (2)—
 - (A) in subparagraph (A), by striking ‘Acts’ and inserting ‘Acts, or otherwise made available for obligation,’; and
 - (B) in subparagraph (B), by striking ‘over such costs for fiscal year 1992’ and inserting ‘over such costs, excluding costs paid from fees collected under this section, for fiscal year 1997’; and

- (3) by striking paragraph (3) and inserting the following:
- ‘(3) AUTHORIZATION OF APPROPRIATIONS- There are authorized to be appropriated for fees under this section—
- ‘(A) \$106,800,000 for fiscal year 1998;
 - ‘(B) \$109,200,000 for fiscal year 1999;
 - ‘(C) \$109,200,000 for fiscal year 2000;
 - ‘(D) \$114,000,000 for fiscal year 2001; and
 - ‘(E) \$110,100,000 for fiscal year 2002, as adjusted to reflect adjustments in the total fee revenues made under this section and changes in the total amounts collected by application, supplement, establishment, and product fees.
- ‘(4) OFFSET- Any amount of fees collected for a fiscal year under this section that exceeds the amount of fees specified in appropriation Acts for such fiscal year shall be credited to the appropriation account of the Food and Drug Administration as provided in paragraph (1), and shall be subtracted from the amount of fees that would otherwise be authorized to be collected under this section pursuant to appropriation Acts for a subsequent fiscal year.’.
- (g) REQUIREMENT FOR WRITTEN REQUESTS FOR WAIVERS, REDUCTIONS, AND REFUNDS- Section 736 (21 U.S.C. 379h) is amended—
- (1) by redesignating subsection (i) as subsection (j); and
 - (2) by inserting after subsection (h) the following:
 - ‘(i) WRITTEN REQUESTS FOR WAIVERS, REDUCTIONS, AND REFUNDS- To qualify for consideration for a waiver or reduction under subsection (d), or for a refund of any fee collected in accordance with subsection (a), a person shall submit to the Secretary a written request for such waiver, reduction, or refund not later than 180 days after such fee is due.’
 - (h) SPECIAL RULE FOR WAIVERS AND REFUNDS- Any requests for waivers or refunds for fees assessed under section 736 of the Federal Food, Drug and Cosmetic Act (42 U.S.C. 379h) prior to the date of enactment of this Act shall be submitted in writing to the Secretary of Health and Human Services within 1 year after the date of enactment of this Act. Any requests for waivers or refunds pertaining to a fee for a human drug application or supplement accepted for filing prior to October 1, 1997 or to a product or establishment fee required by such Act for a fiscal year prior to fiscal year 1998, shall be evaluated according to the terms of the Prescription Drug User Fee Act of 1992 (as in effect on September 30, 1997) and part 2 of subchapter C of chapter VII of the Federal Food, Drug and Cosmetic Act (as in effect on September 30, 1997). The term ‘person’ in such Acts shall continue to include an affiliate thereof.

SEC. 104. ANNUAL REPORTS.

- (a) PERFORMANCE REPORT- Beginning with fiscal year 1998, not later than

60 days after the end of each fiscal year during which fees are collected under part 2 of subchapter C of chapter VII of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 379g et seq.), the Secretary of Health and Human Services shall prepare and submit to the Committee on Commerce of the House of Representatives and the Committee on Labor and Human Resources of the Senate a report concerning the progress of the Food and Drug Administration in achieving the goals identified in the letters described in section 101(4) during such fiscal year and the future plans of the Food and Drug Administration for meeting the goals.

- (b) FISCAL REPORT- Beginning with fiscal year 1998, not later than 120 days after the end of each fiscal year during which fees are collected under the part described in subsection (a), the Secretary of Health and Human Services shall prepare and submit to the Committee on Commerce of the House of Representatives and the Committee on Labor and Human Resources of the Senate a report on the implementation of the authority for such fees during such fiscal year and the use, by the Food and Drug Administration, of the fees collected during such fiscal year for which the report is made.

SEC. 105. SAVINGS.

Notwithstanding section 105 of the Prescription Drug User Fee Act of 1992, the Secretary shall retain the authority to assess and collect any fee required by part 2 of subchapter C of chapter VII of the Federal Food, Drug and Cosmetic Act for a human drug application or supplement accepted for filing prior to October 1, 1997, and to assess and collect any product or establishment fee required by such Act for a fiscal year prior to fiscal year 1998.

SEC. 106. EFFECTIVE DATE.

The amendments made by this subtitle shall take effect October 1, 1997.

SEC. 107. TERMINATION OF EFFECTIVENESS.

The amendments made by sections 102 and 103 cease to be effective October 1, 2002, and section 104 ceases to be effective 120 days after such date.

SUBTITLE B—OTHER IMPROVEMENTS

SEC. 111. PEDIATRIC STUDIES OF DRUGS.

Chapter V (21 U.S.C. 351 et seq.) is amended by inserting after section 505 the following:

‘SEC. 505A. PEDIATRIC STUDIES OF DRUGS.

- ‘(a) MARKET EXCLUSIVITY FOR NEW DRUGS- If, prior to approval of an application that is submitted under section 505(b)(1), the Secretary determines that information relating to the use of a new drug in the pediatric population

may produce health benefits in that population, the Secretary makes a written request for pediatric studies (which shall include a timeframe for completing such studies), and such studies are completed within any such timeframe and the reports thereof submitted in accordance with subsection (d)(2) or accepted in accordance with subsection (d)(3)—

‘(1) (A)(i) the period referred to in subsection (c)(3)(D)(ii) of section 505, and in subsection (j)(4)(D)(ii) of such section, is deemed to be five years and six months rather than five years, and the references in subsections (c)(3)(D)(ii) and (j)(4)(D)(ii) of such section to four years, to forty-eight months, and to seven and one-half years are deemed to be four and one-half years, fifty-four months, and eight years, respectively; or

‘(ii) the period referred to in clauses (iii) and (iv) of subsection (c)(3)(D) of such section, and in clauses (iii) and (iv) of subsection (j)(4)(D) of such section, is deemed to be three years and six months rather than three years; and

‘(B) if the drug is designated under section 526 for a rare disease or condition, the period referred to in section 527(a) is deemed to be seven years and six months rather than seven years; and

‘(2) (A) if the drug is the subject of—

‘(i) a listed patent for which a certification has been submitted under subsection (b)(2)(A)(ii) or (j)(2)(A)(vii)(II) of section 505 and for which pediatric studies were submitted prior to the expiration of the patent (including any patent extensions); or

‘(ii) a listed patent for which a certification has been submitted under subsections (b)(2)(A)(iii) or (j)(2)(A)(vii)(III) of section 505, the period during which an application may not be approved under section 505(c)(3) or section 505(j)(4)(B) shall be extended by a period of six months after the date the patent expires (including any patent extensions); or

‘(B) if the drug is the subject of a listed patent for which a certification has been submitted under subsection (b)(2)(A)(iv) or (j)(2)(A)(vii)(IV) of section 505, and in the patent infringement litigation resulting from the certification the court determines that the patent is valid and would be infringed, the period during which an application may not be approved under section 505(c)(3) or section 505(j)(4)(B) shall be extended by a period of six months after the date the patent expires (including any patent extensions).

‘(b) SECRETARY TO DEVELOP LIST OF DRUGS FOR WHICH ADDITIONAL PEDIATRIC INFORMATION MAY BE BENEFICIAL- Not later than 180 days after the date of enactment of the Food and Drug Administration Modernization Act of 1997, the Secretary, after consultation with experts in pediatric research shall develop, prioritize, and publish an initial list of approved drugs for which additional pediatric information may produce health benefits in the pediatric population. The Secretary shall annually update the list.

- ‘(c) MARKET EXCLUSIVITY FOR ALREADY-MARKETED DRUGS- If the Secretary makes a written request to the holder of an approved application under section 505(b)(1) for pediatric studies (which shall include a timeframe for completing such studies) concerning a drug identified in the list described in subsection (b), the holder agrees to the request, the studies are completed within any such timeframe, and the reports thereof are submitted in accordance with subsection (d)(2) or accepted in accordance with subsection (d)(3)—
- ‘(1) (A)(i) the period referred to in subsection (c)(3)(D)(ii) of section 505, and in subsection (j)(4)(D)(ii) of such section, is deemed to be five years and six months rather than five years, and the references in subsections (c)(3)(D)(ii) and (j)(4)(D)(ii) of such section to four years, to forty-eight months, and to seven and one-half years are deemed to be four and one-half years, fifty-four months, and eight years, respectively; or
- ‘(ii) the period referred to in clauses (iii) and (iv) of subsection (c)(3)(D) of such section, and in clauses (iii) and (iv) of subsection (j)(4)(D) of such section, is deemed to be three years and six months rather than three years; and
- ‘(B) if the drug is designated under section 526 for a rare disease or condition, the period referred to in section 527(a) is deemed to be seven years and six months rather than seven years; and
- ‘(2) (A) if the drug is the subject of—
- ‘(i) a listed patent for which a certification has been submitted under subsection (b)(2)(A)(ii) or (j)(2)(A)(vii)(II) of section 505 and for which pediatric studies were submitted prior to the expiration of the patent (including any patent extensions); or
- ‘(ii) a listed patent for which a certification has been submitted under subsection (b)(2)(A)(iii) or (j)(2)(A)(vii)(III) of section 505, the period during which an application may not be approved under section 505(c)(3) or section 505(j)(4)(B) shall be extended by a period of six months after the date the patent expires (including any patent extensions); or
- ‘(B) if the drug is the subject of a listed patent for which a certification has been submitted under subsection (b)(2)(A)(iv) or (j)(2)(A)(vii)(IV) of section 505, and in the patent infringement litigation resulting from the certification the court determines that the patent is valid and would be infringed, the period during which an application may not be approved under section 505(c)(3) or section 505(j)(4)(B) shall be extended by a period of six months after the date the patent expires (including any patent extensions).
- ‘(d) CONDUCT OF PEDIATRIC STUDIES-
- ‘(1) AGREEMENT FOR STUDIES- The Secretary may, pursuant to a written request from the Secretary under subsection (a) or (c), after consultation with—

- ‘(A) the sponsor of an application for an investigational new drug under section 505(i);
 - ‘(B) the sponsor of an application for a new drug under section 505(b)(1); or
 - ‘(C) the holder of an approved application for a drug under section 505(b)(1), agree with the sponsor or holder for the conduct of pediatric studies for such drug. Such agreement shall be in writing and shall include a timeframe for such studies.
- ‘(2) **WRITTEN PROTOCOLS TO MEET THE STUDIES REQUIREMENT-** If the sponsor or holder and the Secretary agree upon written protocols for the studies, the studies requirement of subsection (a) or (c) is satisfied upon the completion of the studies and submission of the reports thereof in accordance with the original written request and the written agreement referred to in paragraph (1). Not later than 60 days after the submission of the report of the studies, the Secretary shall determine if such studies were or were not conducted in accordance with the original written request and the written agreement and reported in accordance with the requirements of the Secretary for filing and so notify the sponsor or holder.
- ‘(3) **OTHER METHODS TO MEET THE STUDIES REQUIREMENT-** If the sponsor or holder and the Secretary have not agreed in writing on the protocols for the studies, the studies requirement of subsection (a) or (c) is satisfied when such studies have been completed and the reports accepted by the Secretary. Not later than 90 days after the submission of the reports of the studies, the Secretary shall accept or reject such reports and so notify the sponsor or holder. The Secretary’s only responsibility in accepting or rejecting the reports shall be to determine, within the 90 days, whether the studies fairly respond to the written request, have been conducted in accordance with commonly accepted scientific principles and protocols, and have been reported in accordance with the requirements of the Secretary for filing.
- ‘(e) **DELAY OF EFFECTIVE DATE FOR CERTAIN APPLICATION-** If the Secretary determines that the acceptance or approval of an application under section 505(b)(2) or 505(j) for a new drug may occur after submission of reports of pediatric studies under this section, which were submitted prior to the expiration of the patent (including any patent extension) or the applicable period under clauses (ii) through (iv) of section 505(c)(3)(D) or clauses (ii) through (iv) of section 505(j)(4)(D), but before the Secretary has determined whether the requirements of subsection (d) have been satisfied, the Secretary shall delay the acceptance or approval under section 505(b)(2) or 505(j) until the determination under subsection (d) is made, but any such delay shall not exceed 90 days. In the event that requirements of this section are satisfied, the applicable six-month period under subsection (a) or (c) shall be deemed to have been running during the period of delay.
- ‘(f) **NOTICE OF DETERMINATIONS ON STUDIES REQUIREMENT-** The Secretary shall publish a notice of any determination that the requirements of

subsection (d) have been met and that submissions and approvals under subsection (b)(2) or (j) of section 505 for a drug will be subject to the provisions of this section.

- ‘(g) DEFINITIONS- As used in this section, the term ‘pediatric studies’ or ‘studies’ means at least one clinical investigation (that, at the Secretary’s discretion, may include pharmacokinetic studies) in pediatric age groups in which a drug is anticipated to be used.
- ‘(h) LIMITATIONS- A drug to which the six-month period under subsection (a) or (b) has already been applied—
 - ‘(1) may receive an additional six-month period under subsection (c)(1)(A)(ii) for a supplemental application if all other requirements under this section are satisfied, except that such a drug may not receive any additional such period under subsection (c)(2); and
 - ‘(2) may not receive any additional such period under subsection (c)(1)(B).
 - ‘(i) RELATIONSHIP TO REGULATIONS- Notwithstanding any other provision of law, if any pediatric study is required pursuant to regulations promulgated by the Secretary and such study meets the completeness, timeliness, and other requirements of this section, such study shall be deemed to satisfy the requirement for market exclusivity pursuant to this section.
 - ‘(j) SUNSET- A drug may not receive any six-month period under subsection (a) or (c) unless the application for the drug under section 505(b)(1) is submitted on or before January 1, 2002. After January 1, 2002, a drug shall receive a six-month period under subsection (c) if—
 - ‘(1) the drug was in commercial distribution as of the date of enactment of the Food and Drug Administration Modernization Act of 1997;
 - ‘(2) the drug was included by the Secretary on the list under subsection (b) as of January 1, 2002;
 - ‘(3) the Secretary determines that there is a continuing need for information relating to the use of the drug in the pediatric population and that the drug may provide health benefits in that population; and
 - ‘(4) all requirements of this section are met.
- ‘(k) REPORT- The Secretary shall conduct a study and report to Congress not later than January 1, 2001, based on the experience under the program established under this section. The study and report shall examine all relevant issues, including—
 - ‘(1) the effectiveness of the program in improving information about important pediatric uses for approved drugs;
 - ‘(2) the adequacy of the incentive provided under this section;
 - ‘(3) the economic impact of the program on taxpayers and consumers, including the impact of the lack of lower cost generic drugs on patients, including on lower income patients; and
 - ‘(4) any suggestions for modification that the Secretary determines to be appropriate.’.

SEC. 112. EXPEDITING STUDY AND APPROVAL OF FAST TRACK DRUGS.

- (a) IN GENERAL- Chapter V (21 U.S.C. 351 et seq.), as amended by section 125, is amended by inserting before section 508 the following:

‘SEC. 506. FAST TRACK PRODUCTS.

‘(a) DESIGNATION OF DRUG AS A FAST TRACK PRODUCT—

- ‘(1) IN GENERAL- The Secretary shall, at the request of the sponsor of a new drug, facilitate the development and expedite the review of such drug if it is intended for the treatment of a serious or life-threatening condition and it demonstrates the potential to address unmet medical needs for such a condition. (In this section, such a drug is referred to as a ‘fast track product’.)
- ‘(2) REQUEST FOR DESIGNATION- The sponsor of a new drug may request the Secretary to designate the drug as a fast track product. A request for the designation may be made concurrently with, or at any time after, submission of an application for the investigation of the drug under section 505(i) or section 351(a)(3) of the Public Health Service Act.
- ‘(3) DESIGNATION- Within 60 calendar days after the receipt of a request under paragraph (2), the Secretary shall determine whether the drug that is the subject of the request meets the criteria described in paragraph (1). If the Secretary finds that the drug meets the criteria, the Secretary shall designate the drug as a fast track product and shall take such actions as are appropriate to expedite the development and review of the application for approval of such product.

‘(b) APPROVAL OF APPLICATION FOR A FAST TRACK PRODUCT-

- ‘(1) IN GENERAL- The Secretary may approve an application for approval of a fast track product under section 505(c) or section 351 of the Public Health Service Act upon a determination that the product has an effect on a clinical endpoint or on a surrogate endpoint that is reasonably likely to predict clinical benefit.
- ‘(2) LIMITATION- Approval of a fast track product under this subsection may be subject to the requirements—
- ‘(A) that the sponsor conduct appropriate post-approval studies to validate the surrogate endpoint or otherwise confirm the effect on the clinical endpoint; and
- ‘(B) that the sponsor submit copies of all promotional materials related to the fast track product during the proapproval review period and, following approval and for such period thereafter as the Secretary determines to be appropriate, at least 30 days prior to dissemination of the materials.
- ‘(3) EXPEDITED WITHDRAWAL OF APPROVAL- The Secretary may withdraw approval of a fast track product using expedited procedures (as

prescribed by the Secretary in regulations which shall include an opportunity for an informal hearing) if—

- ‘(A) the sponsor fails to conduct any required post-approval study of the fast track drug with due diligence;
- ‘(B) a post-approval study of the fast track product fails to verify clinical benefit of the product;
- ‘(C) other evidence demonstrates that the fast track product is not safe or effective under the conditions of use; or
- ‘(D) the sponsor disseminates false or misleading promotional materials with respect to the product.

‘(c) REVIEW OF INCOMPLETE APPLICATIONS FOR APPROVAL OF A FAST TRACK PRODUCT-

- ‘(1) IN GENERAL- If the Secretary determines, after preliminary evaluation of clinical data submitted by the sponsor, that a fast track product may be effective, the Secretary shall evaluate for filing, and may commence review of portions of, an application for the approval of the product before the sponsor submits a complete application. The Secretary shall commence such review only if the applicant—

- ‘(A) provides a schedule for submission of information necessary to make the application complete; and

- ‘(B) pays any fee that may be required under section 736.

- ‘(2) EXCEPTION- Any time period for review of human drug applications that has been agreed to by the Secretary and that has been set forth in goals identified in letters of the Secretary (relating to the use of fees collected under section 736 to expedite the drug development process and the review of human drug applications) shall not apply to an application submitted under paragraph (1) until the date on which the application is complete.

‘(d) AWARENESS EFFORTS- The Secretary shall—

- ‘(1) develop and disseminate to physicians, patient organizations, pharmaceutical and biotechnology companies, and other appropriate persons a description of the provisions of this section applicable to fast track products; and

- ‘(2) establish a program to encourage the development of surrogate endpoints that are reasonably likely to predict clinical benefit for serious or life-threatening conditions for which there exist significant unmet medical needs.’.

- (b) GUIDANCE- Within 1 year after the date of enactment of this Act, the Secretary of Health and Human Services shall issue guidance for fast track products (as defined in section 506(a)(1) of the Federal Food, Drug and Cosmetic Act) that describes the policies and procedures that pertain to section 506 of such Act.

- (a) IN GENERAL- Section 402 of the Public Health Service Act (42 U.S.C. 282) is amended—

- (1) by redesignating subsections (j) and (k) as subsections (k) and (1), respectively; and

- (2) by inserting after subsection (i) the following:
- ‘(j) (1)(A) The Secretary, acting through the Director of NIH, shall establish, maintain, and operate a data bank of information on clinical trials for drugs for serious or life-threatening diseases and conditions (in this subsection referred to as the ‘data bank’). The activities of the data bank shall be integrated and coordinated with related activities of other agencies of the Department of Health and Human Services, and to the extent practicable, coordinated with other data banks containing similar information.
- ‘(B) The Secretary shall establish the data bank after consultation with the Commissioner of Food and Drugs, the directors of the appropriate agencies of the National Institutes of Health (including the National Library of Medicine), and the Director of the Centers for Disease Control and Prevention.
- ‘(2) In carrying out paragraph (1), the Secretary shall collect, catalog, store, and disseminate the information described in such paragraph. The Secretary shall disseminate such information through information systems, which shall include toll-free telephone communications, available to individuals with serious or life-threatening diseases and conditions, to other members of the public, to health care providers, and to researchers.
- ‘(3) The data bank shall include the following:
- ‘(A) A registry of clinical trials (whether federally or privately funded) of experimental treatments for serious or life-threatening diseases and conditions under regulations promulgated pursuant to section 505(i) of the Federal Food, Drug and Cosmetic Act, which provides a description of the purpose of each experimental drug, either with the consent of the protocol sponsor, or when a trial to test effectiveness begins. Information provided shall consist of eligibility criteria for participation in the clinical trials, a description of the location of trial sites, and a point of contact for those wanting to enroll in the trial, and shall be in a form that can be readily understood by members of the public. Such information shall be forwarded to the data bank by the sponsor of the trial not later than 21 days after the approval of the protocol.
- ‘(B) Information pertaining to experimental treatments for serious or life-threatening diseases and conditions that may be available—
- ‘(i) under a treatment investigational new drug application that has been submitted to the Secretary under section 561(c) of the Federal Food, Drug and Cosmetic Act; or
- ‘(ii) as a Group C cancer drug (as defined by the National Cancer Institute). The data bank may also include information pertaining to the results of clinical trials of such treatments, with the consent of the sponsor, including information concerning potential toxicities or adverse effects associated with the use or administration of such experimental treatments.
- ‘(4) The data bank shall not include information relating to an investigation if the sponsor has provided a detailed certification to the Secretary that

disclosure of such information would substantially interfere with the timely enrollment of subjects in the investigation, unless the Secretary, after the receipt of the certification, provides the sponsor with a detailed written determination that such disclosure would not substantially interfere with such enrollment.

- ‘(5) For the purpose of carrying out this subsection, there are authorized to be appropriated such sums as may be necessary. Fees collected under section 736 of the Federal Food, Drug and Cosmetic Act shall not be used in carrying out this subsection.’.

(b) COLLABORATION AND REPORT-

- (1) IN GENERAL- The Secretary of Health and Human Services, the Director of the National Institutes of Health, and the Commissioner of Food and Drugs shall collaborate to determine the feasibility of including device investigations within the scope of the data bank under section 402(j) of the Public Health Service Act.
- (2) REPORT- Not later than two years after the date of enactment of this section, the Secretary of Health and Human Services shall prepare and submit to the Committee on Labor and Human Resources of the Senate and the Committee on Commerce of the House of Representatives a report—
 - (A) of the public health need, if any, for inclusion of device investigations within the scope of the data bank under section 402(j) of the Public Health Service Act;
 - (B) on the adverse impact, if any, on device innovation and research in the United States if information relating to such device investigations is required to be publicly disclosed; and
 - (C) on such other issues relating to such section 402(j) as the Secretary determines to be appropriate.

SEC. 114. HEALTH CARE ECONOMIC INFORMATION.

- (a) IN GENERAL- Section 502(a) (21 U.S.C. 352(a)) is amended by adding at the end the following: ‘Health care economic information provided to a formulary committee, or other similar entity, in the course of the committee or the entity carrying out its responsibilities for the selection of drugs for managed care or other similar organizations, shall not be considered to be false or misleading under this paragraph if the health care economic information directly relates to an indication approved under section 505 or under section 351(a) of the Public Health Service Act for such drug and is based on competent and reliable scientific evidence. The requirements set forth in section 505(a) or in section 351(a) of the Public Health Service Act shall not apply to health care economic information provided to such a committee or entity in accordance with this paragraph. Information that is relevant to the substantiation of the health care economic information presented pursuant to this paragraph shall be made available to the Secretary upon request. In this paragraph, the term ‘health care economic information’ means any analysis that identifies, measures, or

compares the economic consequences, including the costs of the represented health outcomes, of the use of a drug to the use of another drug, to another health care intervention, or to no intervention.’.

- (b) STUDY AND REPORT- The Comptroller General of the United States shall conduct a study of the implementation of the provisions added by the amendment made by subsection (a). Not later than 4 years and 6 months after the date of enactment of this Act, the Comptroller General of the United States shall prepare and submit to Congress a report containing the findings of the study.

SEC. 115. CLINICAL INVESTIGATIONS.

- (a) CLARIFICATION OF THE NUMBER OF REQUIRED CLINICAL INVESTIGATIONS FOR APPROVAL- Section 505(d) (21 U.S.C. 355(d)) is amended by adding at the end the following: ‘If the Secretary determines, based on relevant science, that data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation) are sufficient to establish effectiveness, the Secretary may consider such data and evidence to constitute substantial evidence for purposes of the preceding sentence.’.
- (b) WOMEN AND MINORITIES- Section 505(b) (1) (21 U.S.C. 355(b) (1)) is amended by adding at the end the following: ‘The Secretary shall, in consultation with the Director of the National Institutes of Health and with representatives of the drug manufacturing industry, review and develop guidance, as appropriate, on the inclusion of women and minorities in clinical trials required by clause (A).’

SEC. 116. MANUFACTURING CHANGES FOR DRUGS.

- (a) IN GENERAL- Chapter V, as amended by section 112, is amended by inserting after section 506 the following section:

‘SEC. 506A. MANUFACTURING CHANGES.

- (a) IN GENERAL- With respect to a drug for which there is in effect an approved application under section 505 or 512 or a license under section 351 of the Public Health Service Act, a change from the manufacturing process approved pursuant to such application or license may be made, and the drug as made with the change may be distributed, if—
 - ‘(1) the holder of the approved application or license (referred to in this section as a ‘holder’) has validated the effects of the change in accordance with subsection (b); and
 - ‘(2) (A) in the case of a major manufacturing change, the holder has complied with the requirements of subsection (c); or
 - ‘(B) in the case of a change that is not a major manufacturing change,

the holder complies with the applicable requirements of subsection (d).

- ‘(b) VALIDATION OF EFFECTS OF CHANGES- For purposes of subsection (a) (1), a drug made with a manufacturing change (whether a major manufacturing change or otherwise) may be distributed only if, before distribution of the drug as so made, the holder involved validates the effects of the change on the identity, strength, quality, purity, and potency of the drug as the identity, strength, quality, purity, and potency may relate to the safety or effectiveness of the drug.

- ‘(c) MAJOR MANUFACTURING CHANGES—

- ‘(1) REQUIREMENT OF SUPPLEMENTAL APPLICATION- For purposes of subsection (a) (2) (A), a drug made with a major manufacturing change may be distributed only if, before the distribution of the drug as so made, the holder involved submits to the Secretary a supplemental application for such change and the Secretary approves the application. The application shall contain such information as the Secretary determines to be appropriate, and shall include the information developed under subsection (b) by the holder in validating the effects of the change.

- ‘(2) CHANGES QUALIFYING AS MAJOR CHANGES- For purposes of subsection (a) (2) (A), a major manufacturing change is a manufacturing change that is determined by the Secretary to have substantial potential to adversely affect the identity, strength, quality, purity, or potency of the drug as they may relate to the safety or effectiveness of a drug. Such a change includes a change that—

- ‘(A) is made in the qualitative or quantitative formulation of the drug involved or in the specifications in the approved application or license referred to in subsection (a) for the drug (unless exempted by the Secretary by regulation or guidance from the requirements of this subsection);

- ‘(B) is determined by the Secretary by regulation or guidance to require completion of an appropriate clinical study demonstrating equivalence of the drug to the drug as manufactured without the change; or

- ‘(C) is another type of change determined by the Secretary by regulation or guidance to have a substantial potential to adversely affect the safety or effectiveness of the drug.

- ‘(d) OTHER MANUFACTURING CHANGES—

- ‘(1) IN GENERAL- For purposes of subsection (a) (2) (B), the Secretary may regulate drugs made with manufacturing changes that are not major manufacturing changes as follows:

- ‘(A) The Secretary may in accordance with paragraph (2) authorize holders to distribute such drugs without submitting a supplemental application for such changes.

- ‘(B) The Secretary may in accordance with paragraph (3) require that, prior to the distribution of such drugs, holders submit to the Secretary supplemental applications for such changes.

- ‘(C) The Secretary may establish categories of such changes and designate categories to which subparagraph (A) applies and categories to which subparagraph (B) applies.
- ‘(2) CHANGES NOT REQUIRING SUPPLEMENTAL APPLICATION—
 - ‘(A) SUBMISSION OF REPORT- A holder making a manufacturing change to which paragraph (1) (A) applies shall submit to the Secretary a report on the change, which shall contain such information as the Secretary determines to be appropriate, and which shall include the information developed under subsection (b) by the holder in validating the effects of the change. The report shall be submitted by such date as the Secretary may specify.
 - ‘(B) AUTHORITY REGARDING ANNUAL REPORTS- In the case of a holder that during a single year makes more than one manufacturing change to which paragraph (1) (A) applies, the Secretary may in carrying out subparagraph (A) authorize the holder to comply with such subparagraph by submitting a single report for the year that provides the information required in such subparagraph for all the changes made by the holder during the year.
- ‘(3) CHANGES REQUIRING SUPPLEMENTAL APPLICATION—
 - ‘(A) SUBMISSION OF SUPPLEMENTAL APPLICATION- The supplemental application required under paragraph (1) (B) for a manufacturing change shall contain such information as the Secretary determines to be appropriate, which shall include the information developed under subsection (b) by the holder in validating the effects of the change.
 - ‘(B) AUTHORITY FOR DISTRIBUTION- In the case of a manufacturing change to which paragraph (1) (B) applies:
 - ‘(i) The holder involved may commence distribution of the drug involved 30 days after the Secretary receives the supplemental application under such paragraph, unless the Secretary notifies the holder within such 30-day period that prior approval of the application is required before distribution may be commenced.
 - ‘(ii) The Secretary may designate a category of such changes for the purpose of providing that, in the case of a change that is in such category, the holder involved may commence distribution of the drug involved upon the receipt by the Secretary of a supplemental application for the change.
 - ‘(iii) If the Secretary disapproves the supplemental application, the Secretary may order the manufacturer to cease the distribution of the drugs that have been made with the manufacturing change.’.
- (b) TRANSITION RULE- The amendment made by subsection (a) takes effect upon the effective date of regulations promulgated by the Secretary of Health and Human Services to implement such amendment, or upon the expiration

of the 24-month period beginning on the date of the enactment of this Act, whichever occurs first.

SEC. 117. STREAMLINING CLINICAL RESEARCH ON DRUGS.

Section 505(i) (21 U.S.C. 355(i)) is amended—

- (1) by redesignating paragraphs (1) through (3) as subparagraphs (A) through (C), respectively;
- (2) by inserting ‘(1)’ after ‘(i)’;
- (3) by striking the last two sentences; and
- (4) by inserting after paragraph (1) (as designated by paragraph (2) of this section) the following new paragraphs:
 - ‘(2) Subject to paragraph (3), a clinical investigation of a new drug may begin 30 days after the Secretary has received from the manufacturer or sponsor of the investigation a submission containing such information about the drug and the clinical investigation, including—
 - ‘(A) information on design of the investigation and adequate reports of basic information, certified by the applicant to be accurate reports, necessary to assess the safety of the drug for use in clinical investigation; and
 - ‘(B) adequate information on the chemistry and manufacturing of the drug, controls available for the drug, and primary data tabulations from animal or human studies.
 - ‘(3) (A) At any time, the Secretary may prohibit the sponsor of an investigation from conducting the investigation (referred to in this paragraph as a ‘clinical hold’) if the Secretary makes a determination described in subparagraph (B). The Secretary shall specify the basis for the clinical hold, including the specific information available to the Secretary which served as the basis for such clinical hold, and confirm such determination in writing.
 - ‘(B) For purposes of subparagraph (A), a determination described in this subparagraph with respect to a clinical hold is that—
 - ‘(i) the drug involved represents an unreasonable risk to the safety of the persons who are the subjects of the clinical investigation, taking into account the qualifications of the clinical investigators, information about the drug, the design of the clinical investigation, the condition for which the drug is to be investigated, and the health status of the subjects involved; or
 - ‘(ii) the clinical hold should be issued for such other reasons as the Secretary may by regulation establish (including reasons established by regulation before the date of the enactment of the Food and Drug Administration Modernization Act of 1997).
 - ‘(C) Any written request to the Secretary from the sponsor of an investigation that a clinical hold be removed shall receive a decision, in

writing and specifying the reasons therefor, within 30 days after receipt of such request. Any such request shall include sufficient information to support the removal of such clinical hold.

- ‘(4) Regulations under paragraph (1) shall provide that such exemption shall be conditioned upon the manufacturer, or the sponsor of the investigation, requiring that experts using such drugs for investigational purposes certify to such manufacturer or sponsor that they will inform any human beings to whom such drugs, or any controls used in connection therewith, are being administered, or their representatives, that such drugs are being used for investigational purposes and will obtain the consent of such human beings or their representatives, except where it is not feasible or it is contrary to the best interests of such human beings. Nothing in this subsection shall be construed to require any clinical investigator to submit directly to the Secretary reports on the investigational use of drugs.’.

SEC. 118. DATA REQUIREMENTS FOR DRUGS AND BIOLOGICS.

Within 12 months after the date of enactment of this Act, the Secretary of Health and Human Services, acting through the Commissioner of Food and Drugs, shall issue guidance that describes when abbreviated study reports may be submitted, in lieu of full reports, with a new drug application under section 505(b) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 355(b)) and with a biologics license application under section 351 of the Public Health Service Act (42 U.S.C. 262) for certain types of studies. Such guidance shall describe the kinds of studies for which abbreviated reports are appropriate and the appropriate abbreviated report formats.

SEC. 119. CONTENT AND REVIEW OF APPLICATIONS.

- (a) SECTION 595(b)- Section 505(b) (21 U.S.C. 355(b)) is amended by adding at the end the following:

‘(4) (A) The Secretary shall issue guidance for the individuals who review applications submitted under paragraph (1) or under section 351 of the Public Health Service Act, which shall relate to promptness in conducting the review, technical excellence, lack of bias and conflict of interest, and knowledge of regulatory and scientific standards, and which shall apply equally to all individuals who review such applications.

‘(B) The Secretary shall meet with a sponsor of an investigation or an applicant for approval for a drug under this subsection or section 351 of the Public Health Service Act if the sponsor or applicant makes a reasonable written request for a meeting for the purpose of reaching agreement on the design and size of clinical trials intended to form the primary basis of an effectiveness claim. The sponsor or applicant shall provide information necessary for discussion and agreement on the design and size of the clinical trials. Minutes of any such meeting shall be prepared by the Secretary and made available to the sponsor or applicant upon request.

- ‘(C) Any agreement regarding the parameters of the design and size of clinical trials of a new drug under this paragraph that is reached between the Secretary and a sponsor or applicant shall be reduced to writing and made part of the administrative record by the Secretary. Such agreement shall not be changed after the testing begins, except—
 - ‘(i) with the written agreement of the sponsor or applicant; or
 - ‘(ii) pursuant to a decision, made in accordance with subparagraph (D) by the director of the reviewing division, that a substantial scientific issue essential to determining the safety or effectiveness of the drug has been identified after the testing has begun.
- ‘(D) A decision under subparagraph (C) (ii) by the director shall be in writing and the Secretary shall provide to the sponsor or applicant an opportunity for a meeting at which the director and the sponsor or applicant will be present and at which the director will document the scientific issue involved.
- ‘(E) The written decisions of the reviewing division shall be binding upon, and may not directly or indirectly be changed by, the field or compliance division personnel unless such field or compliance division personnel demonstrate to the reviewing division why such decision should be modified.
- ‘(F) No action by the reviewing division may be delayed because of the unavailability of information from or action by field personnel unless the reviewing division determines that a delay is necessary to assure the marketing of a safe and effective drug.
- ‘(G) For purposes of this paragraph, the reviewing division is the division responsible for the review of an application for approval of a drug under this subsection or section 351 of the Public Health Service Act (including all scientific and medical matters, chemistry, manufacturing, and controls).’.

(b) SECTION 505(j)-

- (1) AMENDMENT- Section 505(j) (21 U.S.C. 355(j)) is amended—
 - (A) by redesignating paragraphs (3) through (8) as paragraphs (4) through (9), respectively; and
 - (B) by adding after paragraph (2) the following:
- ‘(3) (A) The Secretary shall issue guidance for the individuals who review applications submitted under paragraph (1), which shall relate to promptness in conducting the review, technical excellence, lack of bias and conflict of interest, and knowledge of regulatory and scientific standards, and which shall apply equally to all individuals who review such applications.
- ‘(B) The Secretary shall meet with a sponsor of an investigation or an applicant for approval for a drug under this subsection if the sponsor or applicant makes a reasonable written request for a meeting for the purpose of reaching agreement on the design and size of bioavailability and bioequivalence studies needed for approval of such application. The sponsor or applicant shall provide information nec-

essary for discussion and agreement on the design and size of such studies. Minutes of any such meeting shall be prepared by the Secretary and made available to the sponsor or applicant.

‘(C) Any agreement regarding the parameters of design and size of bio-availability and bioequivalence studies of a drug under this paragraph that is reached between the Secretary and a sponsor or applicant shall be reduced to writing and made part of the administrative record by the Secretary. Such agreement shall not be changed after the testing begins, except—

‘(i) with the written agreement of the sponsor or applicant; or

‘(ii) pursuant to a decision, made in accordance with subparagraph (D) by the director of the reviewing division, that a substantial scientific issue essential to determining the safety or effectiveness of the drug has been identified after the testing has begun.

‘(D) A decision under subparagraph (C) (ii) by the director shall be in writing and the Secretary shall provide to the sponsor or applicant an opportunity for a meeting at which the director and the sponsor or applicant will be present and at which the director will document the scientific issue involved.

‘(E) The written decisions of the reviewing division shall be binding upon, and may not directly or indirectly be changed by, the field or compliance office personnel unless such field or compliance office personnel demonstrate to the reviewing division why such decision should be modified.

‘(F) No action by the reviewing division may be delayed because of the unavailability of information from or action by field personnel unless the reviewing division determines that a delay is necessary to assure the marketing of a safe and effective drug.

‘(G) For purposes of this paragraph, the reviewing division is the division responsible for the review of an application for approval of a drug under this subsection (including scientific matters, chemistry, manufacturing, and controls).’.

(2) CONFORMING AMENDMENTS- Section 505(j) (21 U.S.C. 355(j)), as amended by paragraph (1), is further amended—

(A) in paragraph (2) (A) (i), by striking ‘(6)’ and inserting ‘(7)’;

(B) in paragraph (4) (as redesignated in paragraph (1)), by striking ‘(4)’ and inserting ‘(5)’;

(C) in paragraph (4) (I) (as redesignated in paragraph (1)), by striking ‘(5)’ and inserting ‘(6)’; and

(D) in paragraph (7) (C) (as redesignated in paragraph (1)), by striking ‘(5)’ each place it occurs and inserting ‘(6)’.

SEC. 120. SCIENTIFIC ADVISORY PANELS.

Section 505 (21 U.S.C. 355) is amended by adding at the end the following:

‘(n) (1) For the purpose of providing expert scientific advice and recommendations

to the Secretary regarding a clinical investigation of a drug or the approval for marketing of a drug under section 505 or section 351 of the Public Health Service Act, the Secretary shall establish panels of experts or use panels of experts established before the date of enactment of the Food and Drug Administration Modernization Act of 1997, or both.

- ‘(2) The Secretary may delegate the appointment and oversight authority granted under section 904 to a director of a center or successor entity within the Food and Drug Administration.
- ‘(3) The Secretary shall make appointments to each panel established under paragraph (1) so that each panel shall consist of—
 - ‘(A) members who are qualified by training and experience to evaluate the safety and effectiveness of the drugs to be referred to the panel and who, to the extent feasible, possess skill and experience in the development, manufacture, or utilization of such drugs;
 - ‘(B) members with diverse expertise in such fields as clinical and administrative medicine, pharmacy, pharmacology, pharmacoeconomics, biological and physical sciences, and other related professions;
 - ‘(C) a representative of consumer interests, and a representative of interests of the drug manufacturing industry not directly affected by the matter to be brought before the panel; and
 - ‘(D) two or more members who are specialists or have other expertise in the particular disease or condition for which the drug under review is proposed to be indicated.

Scientific, trade, and consumer organizations shall be afforded an opportunity to nominate individuals for appointment to the panels. No individual who is in the regular full-time employ of the United States and engaged in the administration of this Act may be a voting member of any panel. The Secretary shall designate one of the members of each panel to serve as chairman thereof.

- ‘(4) Each member of a panel shall publicly disclose all conflicts of interest that member may have with the work to be undertaken by the panel. No member of a panel may vote on any matter where the member or the immediate family of such member could gain financially from the advice given to the Secretary. The Secretary may grant a waiver of any conflict of interest requirement upon public disclosure of such conflict of interest if such waiver is necessary to afford the panel essential expertise, except that the Secretary may not grant a waiver for a member of a panel when the member’s own scientific work is involved.
- ‘(5) The Secretary shall, as appropriate, provide education and training to each new panel member before such member participates in a panel’s activities, including education regarding requirements under this Act and related regulations of the Secretary, and the administrative processes and procedures related to panel meetings.
- ‘(6) Panel members (other than officers or employees of the United States), while attending meetings or conferences of a panel or otherwise engaged in its business, shall be entitled to receive compensation for each day so engaged, including traveltime, at rates to be fixed by the Secretary, but

not to exceed the daily equivalent of the rate in effect for positions classified above grade GS-15 of the General Schedule. While serving away from their homes or regular places of business, panel members may be allowed travel expenses (including per diem in lieu of subsistence) as authorized by section 5703 of title 5, United States Code, for persons in the Government service employed intermittently.

- ‘(7) The Secretary shall ensure that scientific advisory panels meet regularly and at appropriate intervals so that any matter to be reviewed by such a panel can be presented to the panel not more than 60 days after the matter is ready for such review. Meetings of the panel may be held using electronic communication to convene the meetings.
- ‘(8) Within 90 days after a scientific advisory panel makes recommendations on any matter under its review, the Food and Drug Administration official responsible for the matter shall review the conclusions and recommendations of the panel, and notify the affected persons of the final decision on the matter, or of the reasons that no such decision has been reached. Each such final decision shall be documented including the rationale for the decision.’.

SEC. 121. POSITRON EMISSION TOMOGRAPHY.

- (a) REGULATION OF COMPOUNDED POSITRON EMISSION TOMOGRAPHY DRUGS- Section 201 (21 U.S.C. 321) is amended by adding at the end the following:

- ‘(ii) The term ‘compounded positron emission tomography drug’—

- ‘(1) means a drug that—

- ‘(A) exhibits spontaneous disintegration of unstable nuclei by the emission of positrons and is used for the purpose of providing dual photon positron emission tomographic diagnostic images; and

- ‘(B) has been compounded by or on the order of a practitioner who is licensed by a State to compound or order compounding for a drug described in subparagraph (A), and is compounded in accordance with that State’s law, for a patient or for research, teaching, or quality control; and

- ‘(2) includes any nonradioactive reagent, reagent kit, ingredient, nuclide generator, accelerator, target material, electronic synthesizer, or other apparatus or computer program to be used in the preparation of such a drug.’.

- (b) ADULTERATION—

- (1) IN GENERAL- Section 501(a) (21 U.S.C. 351(a)) is amended by striking ‘; or (3)’ and inserting the following: ‘; or (C) if it is a compounded positron emission tomography drug and the methods used in, or the facilities and controls used for, its compounding, processing, packing, or holding do not conform to or are not operated or administered in conformity with the positron emission tomography compounding standards and the official monographs of the United States Pharmacopoeia to assure that

such drug meets the requirements of this Act as to safety and has the identity and strength, and meets the quality and purity characteristics, that it purports or is represented to possess; or (3)’.

- (2) SUNSET- Section 501(a)(2)(C) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 351(a)(2)(C)) shall not apply 4 years after the date of enactment of this Act or 2 years after the date on which the Secretary of Health and Human Services establishes the requirements described in subsection (c)(1)(B), whichever is later.
- (c) REQUIREMENTS FOR REVIEW OF APPROVAL PROCEDURES AND CURRENT GOOD MANUFACTURING PRACTICES FOR POSITRON EMISSION TOMOGRAPHY—
 - (1) PROCEDURES AND REQUIREMENTS—
 - (A) IN GENERAL- In order to take account of the special characteristics of positron emission tomography drugs and the special techniques and processes required to produce these drugs, not later than 2 years after the date of enactment of this Act, the Secretary of Health and Human Services shall establish—
 - (i) appropriate procedures for the approval of positron emission tomography drugs pursuant to section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355); and
 - (ii) appropriate current good manufacturing practice requirements for such drugs.
 - (B) CONSIDERATIONS AND CONSULTATION- In establishing the procedures and requirements required by subparagraph (A), the Secretary of Health and Human Services shall take due account of any relevant differences between not-for-profit institutions that compound the drugs for their patients and commercial manufacturers of the drugs. Prior to establishing the procedures and requirements, the Secretary of Health and Human Services shall consult with patient advocacy groups, professional associations, manufacturers, and physicians and scientists licensed to make or use positron emission tomography drugs.
 - (2) SUBMISSION OF NEW DRUG APPLICATIONS AND ABBREVIATED NEW DRUG APPLICATIONS—
 - (A) IN GENERAL- Except as provided in subparagraph (B), the Secretary of Health and Human Services shall not require the submission of new drug applications or abbreviated new drug applications under subsection (b) or (j) of section 505 (21 U.S.C. 355), for compounded positron emission tomography drugs that are not adulterated drugs described in section 501(a)(2)(C) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 351(a)(2)(C)) (as amended by subsection (b)), for a period of 4 years after the date of enactment of this Act, or for 2 years after the date on which the Secretary establishes procedures and requirements under paragraph (1), whichever is longer.

- (B) EXCEPTION- Nothing in this Act shall prohibit the voluntary submission of such applications or the review of such applications by the Secretary of Health and Human Services. Nothing in this Act shall constitute an exemption for a positron emission tomography drug from the requirements of regulations issued under section 505(i) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 355 (i)).
- (d) REVOCATION OF CERTAIN INCONSISTENT DOCUMENTS- Within 30 days after the date of enactment of this Act, the Secretary of Health and Human Services shall publish in the Federal Register a notice terminating the application of the following notices and rule:
 - (1) A notice entitled 'Regulation of Positron Emission Tomography Radiopharmaceutical Drug Products; Guidance; Public Workshop', published in the Federal Register on February 27, 1995, 60 Fed. Reg. 10594.
 - (2) A notice entitled 'Draft Guideline on the Manufacture of Positron Emission Tomography Radiopharmaceutical Drug Products; Availability', published in the Federal Register on February 27, 1995, 60 Fed. Reg. 10593.
 - (3) A final rule entitled 'Current Good Manufacturing Practice for Finished Pharmaceuticals; Positron Emission Tomography', published in the Federal Register on April 22, 1997, 62 Fed. Reg. 19493 (codified at part 211 of title 21, Code of Federal Regulations).
- (e) DEFINITION- As used in this section, the term 'compounded positron emission tomography drug' has the meaning given the term in section 201 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321).

SEC. 122. REQUIREMENTS FOR RADIOPHARMACEUTICALS.

- (a) REQUIREMENTS-
 - (1) REGULATIONS-
 - (A) PROPOSED REGULATIONS- Not later than 180 days after the date of enactment of this Act, the Secretary of Health and Human Services, after consultation with patient advocacy groups, associations, physicians licensed to use radiopharmaceuticals, and the regulated industry, shall issue proposed regulations governing the approval of radiopharmaceuticals. The regulations shall provide that the determination of the safety and effectiveness of such a radiopharmaceutical under section 505 of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 355) or section 351 of the Public Health Service Act (42 U.S.C. 262) shall include consideration of the proposed use of the radiopharmaceutical in the practice of medicine, the pharmacological and toxicological activity of the radiopharmaceutical (including any carrier or ligand component of the radiopharmaceutical), and the estimated absorbed radiation dose of the radiopharmaceutical.
 - (B) FINAL REGULATIONS- Not later than 18 months after the date

- of enactment of this Act, the Secretary shall promulgate final regulations governing the approval of the radiopharmaceuticals.
- (2) SPECIAL RULE- In the case of a radiopharmaceutical, the indications for which such radiopharmaceutical is approved for marketing may, in appropriate cases, refer to manifestations of disease (such as biochemical, physiological, anatomic, or pathological processes) common to, or present in, one or more disease states.
 - (b) DEFINITION- In this section, the term ‘radiopharmaceutical’ means—
 - (1) an article—
 - (A) that is intended for use in the diagnosis or monitoring of a disease or a manifestation of a disease in humans; and
 - (B) that exhibits spontaneous disintegration of unstable nuclei with the emission of nuclear particles or photons; or
 - (2) any nonradioactive reagent kit or nuclide generator that is intended to be used in the preparation of any such article.

SEC. 123. MODERNIZATION OF REGULATION.

- (a) LICENSES-
 - (1) IN GENERAL- Section 351(a) of the Public Health Service Act (42 U.S.C. 262(a)) is amended to read as follows:
 - ‘(a) (1) No person shall introduce or deliver for introduction into interstate commerce any biological product unless—
 - ‘(A) a biologics license is in effect for the biological product; and
 - ‘(B) each package of the biological product is plainly marked with—
 - ‘(i) the proper name of the biological product contained in the package;
 - ‘(ii) the name, address, and applicable license number of the manufacturer of the biological product; and
 - ‘(iii) the expiration date of the biological product.
 - ‘(2) (A) The Secretary shall establish, by regulation, requirements for the approval, suspension, and revocation of biologics licenses.
 - ‘(B) The Secretary shall approve a biologics license application—
 - ‘(i) on the basis of a demonstration that—
 - ‘(I) the biological product that is the subject of the application is safe, pure, and potent; and
 - ‘(II) the facility in which the biological product is manufactured, processed, packed, or held meets standards designed to assure that the biological product continues to be safe, pure, and potent; and
 - ‘(ii) if the applicant (or other appropriate person) consents to the inspection of the facility that is the subject of the application, in accordance with subsection (c).
 - ‘(3) The Secretary shall prescribe requirements under which a biological product undergoing investigation shall be exempt from the requirements of paragraph (1).’.

- (2) ELIMINATION OF EXISTING LICENSE REQUIREMENT- Section 351(d) of the Public Health Service Act (42 U.S.C. 262(d)) is amended—
 - (A) by striking ‘(d)(1)’ and all that follows through ‘of this section.’;
 - (B) in paragraph (2)—
 - (i) by striking ‘(2)(A) Upon’ and inserting ‘(d)(1) Upon’ and
 - (ii) by redesignating subparagraph (B) as paragraph (2); and
 - (C) in paragraph (2) (as so redesignated by subparagraph (B)(ii))—
 - (i) by striking ‘subparagraph (A)’ and inserting ‘paragraph (1)’; and
 - (ii) by striking ‘this subparagraph’ each place it appears and inserting ‘this paragraph’.
- (b) LABELING- Section 351(b) of the Public Health Service Act (42 U.S.C. 262(b)) is amended to read as follows:
 - ‘(b) No person shall falsely label or mark any package or container of any biological product or alter any label or mark on the package or container of the biological product so as to falsify the label or mark.’.
- (c) INSPECTION- Section 351(c) of the Public Health Service Act (42 U.S.C. 262(c)) is amended by striking ‘virus, serum,’ and all that follows and inserting ‘biological product.’.
- (d) DEFINITION; APPLICATION- Section 351 of the Public Health Service Act (42 U.S.C. 262) is amended by adding at the end the following:
 - ‘(i) In this section, the term ‘biological product’ means a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings.’.
- (e) CONFORMING AMENDMENT- Section 503(g)(4) (21 U.S.C. 353(g)(4)) is amended—
 - (1) in subparagraph (A)—
 - (A) by striking ‘section 351 (a)’ and inserting ‘section 351(i)’; and
 - (B) by striking ‘262(a)’ and inserting ‘262(i)’; and (2) in subparagraph (B)(iii), by striking ‘product or establishment license under subsection (a) or (d)’ and inserting ‘biologics license application under subsection (a)’.
- (f) SPECIAL RULE- The Secretary of Health and Human Services shall take measures to minimize differences in the review and approval of products required to have approved biologics license applications under section 351 of the Public Health Service Act (42 U.S.C. 262) and products required to have approved new drug applications under section 505(b)(1) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 355(b)(1)).
- (g) APPLICATION OF FEDERAL FOOD, DRUG AND COSMETIC ACT- Section 351 of the Public Health Service Act (42 U.S.C. 262), as amended by subsection (d), is further amended by adding at the end the following:

- ‘(j) The Federal Food, Drug and Cosmetic Act applies to a biological product subject to regulation under this section, except that a product for which a license has been approved under subsection (a) shall not be required to have an approved application under section 505 of such Act.’.
- (h) EXAMINATIONS AND PROCEDURES- Paragraph (3) of section 353(d) of the Public Health Service Act (42 U.S.C. 263a(d)) is amended to read as follows:
 - ‘(3) EXAMINATIONS AND PROCEDURES- The examinations and procedures identified in paragraph (2) are laboratory examinations and procedures that have been approved by the Food and Drug Administration for home use or that, as determined by the Secretary, are simple laboratory examinations and procedures that have an insignificant risk of an erroneous result, including those that—
 - ‘(A) employ methodologies that are so simple and accurate as to render the likelihood of erroneous results by the user negligible, or
 - ‘(B) the Secretary has determined pose no unreasonable risk of harm to the patient if performed incorrectly.’.

SEC. 124. PILOT AND SMALL SCALE MANUFACTURE.

- (a) HUMAN DRUGS- Section 505(c) (21 U.S.C. 355(c)) is amended by adding at the end the following:
 - ‘(4) A drug manufactured in a pilot or other small facility may be used to demonstrate the safety and effectiveness of the drug and to obtain approval for the drug prior to manufacture of the drug in a larger facility, unless the Secretary makes a determination that a full scale production facility is necessary to ensure the safety or effectiveness of the drug.’.
- (b) ANIMAL DRUGS- Section 512(c) (21 U.S.C. 360b(c)) is amended by adding at the end the following:
 - ‘(4) A drug manufactured in a pilot or other small facility may be used to demonstrate the safety and effectiveness of the drug and to obtain approval for the drug prior to manufacture of the drug in a larger facility, unless the Secretary makes a determination that a full scale production facility is necessary to ensure the safety or effectiveness of the drug.’.

SEC. 125. INSULIN AND ANTIBIOTICS.

- (a) CERTIFICATION OF DRUGS CONTAINING INSULIN—
 - (1) AMENDMENT- Section 506 (21 U.S.C. 356), as in effect before the date of the enactment of this Act, is repealed.
 - (2) Conforming amendments—
 - (A) Section 301(j) (21 U.S.C. 331(j)) is amended by striking ‘506, 507,’.
 - (B) Subsection (k) of section 502 (21 U.S.C. 352) is repealed.
 - (C) Sections 301(i)(1), 510(j)(1)(A), and 510(j)(1)(D) (21 U.S.C. 331(i)(1), 360(j)(1)(A), 360(j)(1)(D)) are each amended by striking ‘, 506, 507,’.

- (D) Section 801 (d)(1) (21 U.S.C. 381(d)(1)) is amended by inserting after '503(b)' the following: 'or composed wholly or partly of insulin'.
 - (E) Section 8126(h)(2) of title 38, United States Code, is amended by inserting 'or' at the end of subparagraph (B), by striking '; or' at the end of subparagraph (C) and inserting a period, and by striking subparagraph (D).
- (b) CERTIFICATION OF ANTIBIOTICS-
- (1) AMENDMENT- Section 507 (21 U.S.C. 357) is repealed.
 - (2) Conforming amendments—
 - (A) Section 201 (aa) (21 U.S.C. 321(aa)) is amended by striking out 'or 507', section 201(dd) (21 U.S.C. 321 (dd)) is amended by striking '507,', and section 201 (ff)(3)(A) (21 U.S.C. 321 (ff)(3)(A)) is amended by striking ', certified as an antibiotic under section 507,'.
 - (B) Section 301(e) (21 U.S.C. 331(e)) is amended by striking '507(d) or (g),'.
 - (C) Section 306(d)(4)(B)(ii) (21 U.S.C. 335a(d)(4)(B)(ii)) is amended by striking 'or 507'.
 - (D) Section 502 (21 U.S.C. 352) is amended by striking subsection (1).
 - (E) Section 520(1) (21 U.S.C. 360j(1)) is amended by striking paragraph (4) and by striking 'or Antibiotic Drugs' in the subsection heading.
 - (F) Section 525(a) (21 U.S.C. 360aa(a)) is amended by inserting 'or' at the end of paragraph (1), by striking paragraph (2), and by redesignating paragraph (3) as paragraph (2).
 - (G) Section 525(a) (21 U.S.C. 360aa(a)) is amended by striking ', certification of such drug for such disease or condition under section 507,'.
 - (H) Section 526(a)(1) (21 U.S.C. 360bb) is amended by striking 'the submission of an application for certification of the drug under section 507,', by inserting 'or' at the end of subparagraph (A), by striking subparagraph (B), and by redesignating subparagraph (C) as subparagraph (B).
 - (I) Section 526(b) (21 U.S.C. 360bb(b)) is amended—
 - (i) in paragraph (1), by striking ', a certificate was issued for the drug under section 507,'; and
 - (ii) in paragraph (2) by striking ', a certificate has not been issued for the drug under section 507,' and by striking ', approval of an application for certification under section 507,'.
 - (J) Section 527(a) (21 U.S.C. 360cc(a)) is amended by inserting 'or' at the end of paragraph (1), by striking paragraph (2), by redesignating paragraph (3) as paragraph (2), and by striking ', issue another certification under section 507,'.
 - (K) Section 527(b) (21 U.S.C. 360cc(b)) is amended by striking ', if a certification is issued under section 507 for such a drug,', ', of the

issuance of the certification under section 507,’ , ‘, issue another certification under section 507,’ , ‘, of such certification,’ , ‘, of the certification,’ , and ‘, issuance of other certifications,’ .

- (L) Section 704(a)(1) (21 U.S.C. 374(a)(1)) is amended by striking ‘, section 507(d) or (g),’ .
- (M) Section 735(1) (21 U.S.C. 379g(1)(C)) is amended by inserting ‘or’ at the end of subparagraph (B), by striking subparagraph (C), and by redesignating subparagraph (D) as subparagraph (C).
- (N) Subparagraphs (A)(ii) and (B) of sections 5(b)(1) of the Orphan Drug Act (21 U.S.C. 360ee(b)(1)(A), 360ee(b)(1)(B)) are each amended by striking ‘or 507’ .
- (O) Section 45C(b)(2)(A)(ii)(II) of the Internal Revenue Code of 1986 is amended by striking ‘or 507’ .
- (P) Section 156(f)(4)(B) of title 35, United States Code, is amended by striking ‘507,’ each place it occurs.
- (c) EXPORTATION- Section 802 (21 U.S.C. 382) is amended by adding at the end the following:
 - ‘(i) Insulin and antibiotic drugs may be exported without regard to the requirements in this section if the insulin and antibiotic drugs meet the requirements of section 801(e)(1).’ .
- (d) TRANSITION-
 - (1) IN GENERAL- An application that was approved by the Secretary of Health and Human Services before the date of the enactment of this Act for the marketing of an antibiotic drug under section 507 of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 357), as in effect on the day before the date of the enactment of this Act, shall, on and after such date of enactment, be considered to be an application that was submitted and filed under section 505(b) of such Act (21 U.S.C. 355(b)) and approved for safety and effectiveness under section 505(c) of such Act (21 U.S.C. 355(c)), except that if such application for marketing was in the form of an abbreviated application, the application shall be considered to have been filed and approved under section 505(j) of such Act (21 U.S.C. 355(j)).
 - (2) EXCEPTION- The following subsections of section 505 (21 U.S.C. 355) shall not apply to any application for marketing in which the drug that is the subject of the application contains an antibiotic drug and the antibiotic drug was the subject of any application for marketing received by the Secretary of Health and Human Services under section 507 of such Act (21 U.S.C. 357) before the date of the enactment of this Act:
 - (A) (i) Subsections (c)(2), (d)(6), (e)(4), (j)(2)(A)(vii), (j)(2)(A)(viii), (j)(2)(B), (j)(4)(B), and (j)(4)(D); and
 - (ii) The third and fourth sentences of subsection (b)(1) (regarding the filing and publication of patent information); and
 - (B) Subsections (b)(2)(A), (b)(2)(B), (b)(3), and (c)(3) if the investigations relied upon by the applicant for approval of the application

were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted.

- (3) PUBLICATION- For purposes of this section, the Secretary is authorized to make available to the public the established name of each antibiotic drug that was the subject of any application for marketing received by the Secretary for Health and Human Services under section 507 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 357) before the date of enactment of this Act.
- (e) DEFINITION- Section 201 (21 U.S.C. 321), as amended by section 121(a)(1), is further amended by adding at the end the following:
 - ‘(jj) The term ‘antibiotic drug’ means any drug (except drugs for use in animals other than humans) composed wholly or partly of any kind of penicillin, streptomycin, chlortetracycline, chloramphenicol, bacitracin, or any other drug intended for human use containing any quantity of any chemical substance which is produced by a micro-organism and which has the capacity to inhibit or destroy micro-organisms in dilute solution (including a chemically synthesized equivalent of any such substance) or any derivative thereof.’.

SEC. 126. ELIMINATION OF CERTAIN LABELING REQUIREMENTS.

- (a) PRESCRIPTION DRUGS- Section 503(b)(4) (21 U.S.C. 353(b)(4)) is amended to read as follows:
 - ‘(4) (A) A drug that is subject to paragraph (1) shall be deemed to be misbranded if at any time prior to dispensing the label of the drug fails to bear, at a minimum, the symbol ‘Rx only’.
 - ‘(B) A drug to which paragraph (1) does not apply shall be deemed to be misbranded if at any time prior to dispensing the label of the drug bears the symbol described in subparagraph (A).’.
- (b) MISBRANDED DRUG- Section 502(d) (21 U.S.C. 352(d)) is repealed.
- (c) CONFORMING AMENDMENTS-
 - (1) Section 503(b)(1) (21 U.S.C. 353(b)(1)) is amended—
 - (A) by striking subparagraph (A); and
 - (B) by redesignating subparagraphs (B) and (C) as subparagraphs (A) and (B), respectively.
 - (2) Section 503(b)(3) (21 U.S.C. 353(b)(3)) is amended by striking ‘section 502(d) and’.
 - (3) Section 102(9)(A) of the Controlled Substances Act (21 U.S.C. 802(9)(A)) is amended—
 - (A) in clause (i), by striking ‘(i)’; and
 - (B) by striking ‘(ii)’ and all that follows.
- (a) AMENDMENT- Chapter V is amended by inserting after section 503 (21 U.S.C. 353) the following:

‘SEC. 503A. PHARMACY COMPOUNDING.

- ‘(a) IN GENERAL- Sections 501(a)(2)(B), 502(f)(1), and 505 shall not apply to

a drug product if the drug product is compounded for an identified individual patient based on the unsolicited receipt of a valid prescription order or a notation, approved by the prescribing practitioner, on the prescription order that a compounded product is necessary for the identified patient, if the drug product meets the requirements of this section, and if the compounding—

‘(1) is by—

‘(A) a licensed pharmacist in a State licensed pharmacy or a Federal facility, or

‘(B) a licensed physician, on the prescription order for such individual patient made by a licensed physician or other licensed practitioner authorized by State law to prescribe drugs; or

‘(2) (A) is by a licensed pharmacist or licensed physician in limited quantities before the receipt of a valid prescription order for such individual patient; and

‘(B) is based on a history of the licensed pharmacist or licensed physician receiving valid prescription orders for the compounding of the drug product, which orders have been generated solely within an established relationship between—

‘(i) the licensed pharmacist or licensed physician; and

‘(ii) (I) such individual patient for whom the prescription order will be provided; or

‘(II) the physician or other licensed practitioner who will write such prescription order.

‘(b) COMPOUNDED DRUG—

‘(1) LICENSED PHARMACIST AND LICENSED PHYSICIAN- A drug product may be compounded under subsection (a) if the licensed pharmacist or licensed physician—

‘(A) compounds the drug product using bulk drug substances, as defined in regulations of the Secretary published at section 207.3(a)(4) of title 21 of the Code of Federal Regulations—

‘(i) that—

‘(I) comply with the standards of an applicable United States Pharmacopoeia or National Formulary monograph, if a monograph exists, and the United States Pharmacopoeia chapter on pharmacy compounding;

‘(II) if such a monograph does not exist, are drug substances that are components of drugs approved by the Secretary; or

‘(III) if such a monograph does not exist and the drug substance is not a component of a drug approved by the Secretary, that appear on a list developed by the Secretary through regulations issued by the Secretary under subsection (d);

‘(ii) that are manufactured by an establishment that is registered under section 510 (including a foreign establishment that is registered under section 510(i)); and

‘(iii) that are accompanied by valid certificates of analysis for each bulk drug substance;

‘(B) compounds the drug product using ingredients (other than bulk drug substances) that comply with the standards of an applicable

United States Pharmacopoeia or National Formulary monograph, if a monograph exists, and the United States Pharmacopoeia chapter on pharmacy compounding;

‘(C) does not compound a drug product that appears on a list published by the Secretary in the Federal Register of drug products that have been withdrawn or removed from the market because such drug products or components of such drug products have been found to be unsafe or not effective; and

‘(D) does not compound regularly or in inordinate amounts (as defined by the Secretary) any drug products that are essentially copies of a commercially available drug product.

‘(2) DEFINITION- For purposes of paragraph (1)(D), the term ‘essentially a copy of a commercially available drug product’ does not include a drug product in which there is a change, made for an identified individual patient, which produces for that patient a significant difference, as determined by the prescribing practitioner, between the compounded drug and the comparable commercially available drug product.

‘(3) DRUG PRODUCT- A drug product may be compounded under subsection (a) only if—

‘(A) such drug product is not a drug product identified by the Secretary by regulation as a drug product that presents demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety or effectiveness of that drug product; and

‘(B) such drug product is compounded in a State—

‘(i) that has entered into a memorandum of understanding with the Secretary which addresses the distribution of inordinate amounts of compounded drug products interstate and provides for appropriate investigation by a State agency of complaints relating to compounded drug products distributed outside such State; or

‘(ii) that has not entered into the memorandum of understanding described in clause (i) and the licensed pharmacist, licensed pharmacy, or licensed physician distributes (or causes to be distributed) compounded drug products out of the State in which they are compounded in quantities that do not exceed 5 percent of the total prescription orders dispensed or distributed by such pharmacy or physician.

The Secretary shall, in consultation with the National Association of Boards of Pharmacy, develop a standard memorandum of understanding for use by the States in complying with subparagraph (B)(i).

‘(c) ADVERTISING AND PROMOTION- A drug may be compounded under subsection (a) only if the pharmacy, licensed pharmacist, or licensed physician does not advertise or promote the compounding of any particular drug, class of drug, or type of drug. The pharmacy, licensed pharmacist, or licensed physi-

cian may advertise and promote the compounding service provided by the licensed pharmacist or licensed physician.

‘(d) REGULATIONS—

‘(1) IN GENERAL- The Secretary shall issue regulations to implement this section. Before issuing regulations to implement subsections (b)(1)(A)(i)(III), (b)(1)(C), or (b)(3)(A), the Secretary shall convene and consult an advisory committee on compounding unless the Secretary determines that the issuance of such regulations before consultation is necessary to protect the public health. The advisory committee shall include representatives from the National Association of Boards of Pharmacy, the United States Pharmacopoeia, pharmacy, physician, and consumer organizations, and other experts selected by the Secretary.

‘(2) LIMITING COMPOUNDING- The Secretary, in consultation with the United States Pharmacopoeia Convention, Incorporated, shall promulgate regulations identifying drug substances that may be used in compounding under subsection (b)(1)(A)(i)(III) for which a monograph does not exist or which are not components of drug products approved by the Secretary. The Secretary shall include in the regulation the criteria for such substances, which shall include historical use, reports in peer reviewed medical literature, or other criteria the Secretary may identify.

‘(e) APPLICATION- This section shall not apply to—

‘(1) compounded positron emission tomography drugs as defined in section 201 (ii); or

‘(2) radiopharmaceuticals.

‘(f) DEFINITION- As used in this section, the term ‘compounding’ does not include mixing, reconstituting, or other such acts that are performed in accordance with directions contained in approved labeling provided by the product’s manufacturer and other manufacturer directions consistent with that labeling.’.

(b) EFFECTIVE DATE- Section 503A of the Federal Food, Drug and Cosmetic Act, added by subsection (a), shall take effect upon the expiration of the 1-year period beginning on the date of the enactment of this Act.

SEC. 128. REAUTHORIZATION OF CLINICAL PHARMACOLOGY PROGRAM.

Section 2 of Public Law 102-222 (105 Stat. 1677) is amended—

- (1) in subsection (a), by striking ‘a grant’ and all that follows through ‘Such grant’ and inserting the following: ‘grants for a pilot program for the training of individuals in clinical pharmacology at appropriate medical schools. Such grants’; and
- (2) in subsection (b), by striking ‘to carry out this section’ and inserting’, and for fiscal years 1998 through 2002 \$3,000,000 for each fiscal year, to carry out this section’.

SEC. 129. REGULATIONS FOR SUNSCREEN PRODUCTS.

Not later than 18 months after the date of enactment of this Act, the Secretary of Health and Human Services shall issue regulations for over-the-counter sunscreen products for the prevention or treatment of sunburn.

SEC. 130. REPORTS OF POSTMARKETING APPROVAL STUDIES.

- (a) IN GENERAL- Chapter V, as amended by section 116, is further amended by inserting after section 506A the following:

‘SEC. 506B. REPORTS OF POSTMARKETING STUDIES.

‘(a) SUBMISSION—

‘(1) IN GENERAL- A sponsor of a drug that has entered into an agreement with the Secretary to conduct a postmarketing study of a drug shall submit to the Secretary, within 1 year after the approval of such drug and annually thereafter until the study is completed or terminated, a report of the progress of the study or the reasons for the failure of the sponsor to conduct the study. The report shall be submitted in such form as is prescribed by the Secretary in regulations issued by the Secretary.

‘(2) AGREEMENTS PRIOR TO EFFECTIVE DATE- Any agreement entered into between the Secretary and a sponsor of a drug, prior to the date of enactment of the Food and Drug Administration Modernization Act of 1997, to conduct a postmarketing study of a drug shall be subject to the requirements of paragraph (1). An initial report for such an agreement shall be submitted within 6 months after the date of the issuance of the regulations under paragraph (1).

‘(b) CONSIDERATION OF INFORMATION AS PUBLIC INFORMATION-Any information pertaining to a report described in subsection (a) shall be considered to be public information to the extent that the information is necessary—

‘(1) to identify the sponsor; and

‘(2) to establish the status of a study described in subsection (a) and the reasons, if any, for any failure to carry out the study.

‘(c) STATUS OF STUDIES AND REPORTS- The Secretary shall annually develop and publish in the Federal Register a report that provides information on the status of the postmarketing studies—

‘(1) that sponsors have entered into agreements to conduct; and

‘(2) for which reports have been submitted under subsection (a)(1).’.

(b) REPORT TO CONGRESSIONAL COMMITTEES- Not later than October 1, 2001, the Secretary shall prepare and submit to the Committee on Labor and Human Resources of the Senate and the Committee on Commerce of the House of Representatives a report containing—

- (1) a summary of the reports submitted under section 506B of the Federal Food, Drug and Cosmetic Act;
 - (2) an evaluation of—
 - (A) the performance of the sponsors referred to in such section in fulfilling the agreements with respect to the conduct of postmarketing studies described in such section of such Act; and
 - (B) the timeliness of the Secretary's review of the postmarketing studies; and
 - (3) any legislative recommendations respecting the postmarketing studies.
- (a) IN GENERAL- Chapter V, as amended by section 130, is further amended by inserting after section 506B the following:.

‘SEC. 506C. DISCONTINUANCE OF A LIFE SAVING PRODUCT.

- ‘(a) IN GENERAL- A manufacturer that is the sole manufacturer of a drug—
 - (1) that is—
 - ‘(A) life-supporting;
 - ‘(B) life-sustaining; or
 - ‘(C) intended for use in the prevention of a debilitating disease or condition;
 - ‘(2) for which an application has been approved under section 505(b) or 505(j); and
 - ‘(3) that is not a product that was originally derived from human tissue and was replaced by a recombinant product, shall notify the Secretary of a discontinuance of the manufacture of the drug at least 6 months prior to the date of the discontinuance.
- ‘(b) REDUCTION IN NOTIFICATION PERIOD- The notification period required under subsection (a) for a manufacturer may be reduced if the manufacturer certifies to the Secretary that good cause exists for the reduction, such as a situation in which—
 - ‘(1) a public health problem may result from continuation of the manufacturing for the 6-month period;
 - ‘(2) a biomaterials shortage prevents the continuation of the manufacturing for the 6-month period;
 - ‘(3) a liability problem may exist for the manufacturer if the manufacturing is continued for the 6-month period;
 - ‘(4) continuation of the manufacturing for the 6-month period may cause substantial economic hardship for the manufacturer;
 - ‘(5) the manufacturer has filed for bankruptcy under chapter 7 or 11 of title 11, United States Code; or
 - ‘(6) the manufacturer can continue the distribution of the drug involved for 6 months.
- ‘(c) DISTRIBUTION- To the maximum extent practicable, the Secretary shall distribute information on the discontinuation of the drugs described in subsection (a) to appropriate physician and patient organizations.’.

TITLE II—IMPROVING REGULATION OF DEVICES

SEC. 201. INVESTIGATIONAL DEVICE EXEMPTIONS.

(a) IN GENERAL- Section 520(g) (21 U.S.C. 360j(g)) is amended by adding at the end the following:

‘(6) (A) Not later than 1 year after the date of the enactment of the Food and Drug Administration Modernization Act of 1997, the Secretary shall by regulation establish, with respect to a device for which an exemption under this subsection is in effect, procedures and conditions that, without requiring an additional approval of an application for an exemption or the approval of a supplement to such an application, permit—

‘(i) developmental changes in the device (including manufacturing changes) that do not constitute a significant change in design or in basic principles of operation and that are made in response to information gathered during the course of an investigation; and

‘(ii) changes or modifications to clinical protocols that do not affect—

‘(I) the validity of data or information resulting from the completion of an approved protocol, or the relationship of likely patient risk to benefit relied upon to approve a protocol;

‘(II) the scientific soundness of an investigational plan submitted under paragraph (3)(A); or

‘(III) the rights, safety, or welfare of the human subjects involved in the investigation.

‘(B) Regulations under subparagraph (A) shall provide that a change or modification described in such subparagraph may be made if—

‘(i) the sponsor of the investigation determines, on the basis of credible information (as defined by the Secretary) that the applicable conditions under subparagraph (A) are met; and

‘(ii) the sponsor submits to the Secretary, not later than 5 days after making the change or modification, a notice of the change or modification.

‘(7) (A) In the case of a person intending to investigate the safety or effectiveness of a class III device or any implantable device, the Secretary shall ensure that the person has an opportunity, prior to submitting an application to the Secretary or to an institutional review committee, to submit to the Secretary, for review, an investigational plan (including a clinical protocol). If the applicant submits a written request for a meeting with the Secretary regarding such review, the Secretary shall, not later than 30 days after receiving the request, meet with the applicant for the purpose of reaching agreement regarding the investigational plan (including a clini-

cal protocol). The written request shall include a detailed description of the device, a detailed description of the proposed conditions of use of the device, a proposed plan (including a clinical protocol) for determining whether there is a reasonable assurance of effectiveness, and, if available, information regarding the expected performance from the device.

‘(B) Any agreement regarding the parameters of an investigational plan (including a clinical protocol) that is reached between the Secretary and a sponsor or applicant shall be reduced to writing and made part of the administrative record by the Secretary. Any such agreement shall not be changed, except—

‘(i) with the written agreement of the sponsor or applicant; or

‘(ii) pursuant to a decision, made in accordance with subparagraph (C) by the director of the office in which the device involved is reviewed, that a substantial scientific issue essential to determining the safety or effectiveness of the device involved has been identified.

‘(C) A decision under subparagraph (B)(ii) by the director shall be in writing, and may be made only after the Secretary has provided to the sponsor or applicant an opportunity for a meeting at which the director and the sponsor or applicant are present and at which the director documents the scientific issue involved.’.

(b) ACTION ON APPLICATION- Section 515(d)(1) (B) (21 U.S.C. 360e(d)(1) (B)) is amended by adding at the end the following:

‘(iii) The Secretary shall accept and review statistically valid and reliable data and any other information from investigations conducted under the authority of regulations required by section 520(g) to make a determination of whether there is a reasonable assurance of safety and effectiveness of a device subject to a pending application under this section if—

‘(I) the data or information is derived from investigations of an earlier version of the device, the device has been modified during or after the investigations (but prior to submission of an application under subsection (c)) and such a modification of the device does not constitute a significant change in the design or in the basic principles of operation of the device that would invalidate the data or information; or

‘(II) the data or information relates to a device approved under this section, is available for use under this Act, and is relevant to the design and intended use of the device for which the application is pending.’.

SEC. 202. SPECIAL REVIEW FOR CERTAIN DEVICES.

Section 515(d) (21 U.S.C. 360e(d)) is amended—

- (1) by redesignating paragraph (3) as paragraph (4); and
 - (2) by adding at the end the following:
- ‘(5) In order to provide for more effective treatment or diagnosis of life-threatening or irreversibly debilitating human diseases or conditions, the Secretary shall provide review priority for devices—
- ‘(A) representing breakthrough technologies,
 - ‘(B) for which no approved alternatives exist,
 - ‘(C) which offer significant advantages over existing approved alternatives, or
 - ‘(D) the availability of which is in the best interest of the patients.’.

SEC. 203. EXPANDING HUMANITARIAN USE OF DEVICES.

Section 520(m) (21 U.S.C. 360j(m)) is amended—

- (1) in paragraph (2), by adding after and below subparagraph (C) the following sentences:

‘The request shall be in the form of an application submitted to the Secretary. Not later than 75 days after the date of the receipt of the application, the Secretary shall issue an order approving or denying the application.’;
- (2) in paragraph (4)—
 - (A) in subparagraph (B), by inserting after ‘(2)(A)’ the following: ‘, unless a physician determines in an emergency situation that approval from a local institutional review committee can not be obtained in time to prevent serious harm or death to a patient’; and
 - (B) by adding after and below subparagraph (B) the following:

‘In a case described in subparagraph (B) in which a physician uses a device without an approval from an institutional review committee, the physician shall, after the use of the device, notify the chairperson of the local institutional review committee of such use. Such notification shall include the identification of the patient involved, the date on which the device was used, and the reason for the use.’;
- (3) by amending paragraph (5) to read as follows:

‘(5) The Secretary may require a person granted an exemption under paragraph (2) to demonstrate continued compliance with the requirements of this subsection if the Secretary believes such demonstration to be necessary to protect the public health or if the Secretary has reason to believe that the criteria for the exemption are no longer met.’; and
- (4) by amending paragraph (6) to read as follows:

‘(6) The Secretary may suspend or withdraw an exemption from the effectiveness requirements of sections 514 and 515 for a humanitarian device only after providing notice and an opportunity for an informal hearing.’.

SEC. 204. DEVICE STANDARDS.

- (a) ALTERNATIVE PROCEDURE- Section 514 (21 U.S.C. 360d) is amended by adding at the end the following:

‘RECOGNITION OF A STANDARD

- ‘(c) (1)(A) In addition to establishing a performance standard under this section, the Secretary shall, by publication in the Federal Register, recognize all or part of an appropriate standard established by a nationally or internationally recognized standard development organization for which a person may submit a declaration of conformity in order to meet a premarket submission requirement or other requirement under this Act to which such standard is applicable.
 - ‘(B) If a person elects to use a standard recognized by the Secretary under subparagraph (A) to meet the requirements described in such subparagraph, the person shall provide a declaration of conformity to the Secretary that certifies that the device is in conformity with such standard. A person may elect to use data, or information, other than data required by a standard recognized under subparagraph (A) to meet any requirement regarding devices under this Act.
- ‘(2) The Secretary may withdraw such recognition of a standard through publication of a notice in the Federal Register if the Secretary determines that the standard is no longer appropriate for meeting a requirement regarding devices under this Act.
- ‘(3) (A) Subject to subparagraph (B), the Secretary shall accept a declaration of conformity that a device is in conformity with a standard recognized under paragraph (1) unless the Secretary finds—
 - ‘(i) that the data or information submitted to support such declaration does not demonstrate that the device is in conformity with the standard identified in the declaration of conformity;
 - or
 - ‘(ii) that the standard identified in the declaration of conformity is not applicable to the particular device under review.
- ‘(B) The Secretary may request, at any time, the data or information relied on by the person to make a declaration of conformity with respect to a standard recognized under paragraph (1).
- ‘(C) A person making a declaration of conformity with respect to a standard recognized under paragraph (1) shall maintain the data and information demonstrating conformity of the device to the standard for a period of two years after the date of the classification or approval of the device by the Secretary or a period equal to the expected design life of the device, whichever is longer.’.
- (b) SECTION 301-Section 301 (21 U.S.C. 331) is amended by adding at the end the following:
 - ‘(x) The falsification of a declaration of conformity submitted under section 514(c) or the failure or refusal to provide data or information requested by the Secretary under paragraph (3) of such section.’.
- (c) SECTION 501-Section 501(e) (21 U.S.C. 351 (e)) is amended—
 - (1) by striking ‘(e)’ and inserting ‘(e)(1)’; and
 - (2) by inserting at the end the following:

- ‘(2) If it is declared to be, purports to be, or is represented as, a device that is in conformity with any standard recognized under section 514(c) unless such device is in all respects in conformity with such standard.’.
- (d) CONFORMING AMENDMENTS- Section 514(a) (21 U.S.C. 360d(a)) is amended—
- (1) in paragraph (1), in the second sentence, by striking ‘under this section’ and inserting ‘under subsection (b)’;
 - (2) in paragraph (2), in the matter preceding subparagraph (A), by striking ‘under this section’ and inserting ‘under subsection (b)’;
 - (3) in paragraph (3), by striking ‘under this section’ and inserting ‘under subsection (b)’; and
 - (4) in paragraph (4), in the matter preceding subparagraph (A), by striking ‘this section’ and inserting ‘this subsection and subsection (b)’.
- (a) SECTION 513(a)- Section 513(a)(3) (21 U.S.C. 360c(a)(3)) is amended by adding at the end the following:
- ‘(C) In making a determination of a reasonable assurance of the effectiveness of a device for which an application under section 515 has been submitted, the Secretary shall consider whether the extent of data that otherwise would be required for approval of the application with respect to effectiveness can be reduced through reliance on postmarket controls.
 - ‘(D) (i) The Secretary, upon the written request of any person intending to submit an application under section 515, shall meet with such person to determine the type of valid scientific evidence (within the meaning of subparagraphs (A) and (B)) that will be necessary to demonstrate for purposes of approval of an application the effectiveness of a device for the conditions of use proposed by such person. The written request shall include a detailed description of the device, a detailed description of the proposed conditions of use of the device, a proposed plan for determining whether there is a reasonable assurance of effectiveness, and, if available, information regarding the expected performance from the device. Within 30 days after such meeting, the Secretary shall specify in writing the type of valid scientific evidence that will provide a reasonable assurance that a device is effective under the conditions of use proposed by such person.
 - ‘(ii) Any clinical data, including one or more well-controlled investigations, specified in writing by the Secretary for demonstrating a reasonable assurance of device effectiveness shall be specified as result of a determination by the Secretary that such data are necessary to establish device effectiveness. The Secretary shall consider, in consultation with the applicant, the least burdensome appropriate means of evaluating device effectiveness that would have a reasonable likelihood of resulting in approval.

- ‘(iii) The determination of the Secretary with respect to the specification of valid scientific evidence under clauses (i) and (ii) shall be binding upon the Secretary, unless such determination by the Secretary could be contrary to the public health.’.
- (b) SECTION 513(i)- Section 513(i)(1) (21 U.S.C. 360c(i)(1)) is amended by adding at the end the following:
 - ‘(C) To facilitate reviews of reports submitted to the Secretary under section 510(k), the Secretary shall consider the extent to which reliance on postmarket controls may expedite the classification of devices under subsection (f)(1) of this section.
 - ‘(D) Whenever the Secretary requests information to demonstrate that devices with differing technological characteristics are substantially equivalent, the Secretary shall only request information that is necessary to making substantial equivalence determinations. In making such request, the Secretary shall consider the least burdensome means of demonstrating substantial equivalence and request information accordingly.
 - ‘(E) (i) Any determination by the Secretary of the intended use of a device shall be based upon the proposed labeling submitted in a report for the device under section 510(k). However, when determining that a device can be found substantially equivalent to a legally marketed device, the director of the organizational unit responsible for regulating devices (in this subparagraph referred to as the ‘Director’) may require a statement in labeling that provides appropriate information regarding a use of the device not identified in the proposed labeling if, after providing an opportunity for consultation with the person who submitted such report, the Director determines and states in writing—
 - ‘(I) that there is a reasonable likelihood that the device will be used for an intended use not identified in the proposed labeling for the device; and
 - ‘(II) that such use could cause harm.
 - ‘(ii) Such determination shall—
 - ‘(I) be provided to the person who submitted the report within 10 days from the date of the notification of the Director’s concerns regarding the proposed labeling;
 - ‘(II) specify the limitations on the use of the device not included in the proposed labeling; and
 - ‘(III) find the device substantially equivalent if the requirements of subparagraph (A) are met and if the labeling for such device conforms to the limitations specified in subclause (II).
 - ‘(iii) The responsibilities of the Director under this subparagraph may not be delegated.

‘(iv) This subparagraph has no legal effect after the expiration of the five-year period beginning on the date of the enactment of the Food and Drug Administration Modernization Act of 1997.’.

(c) SECTION 515(d)- Section 515(d) (21 U.S.C. 360e(d)) is amended—

(1) in paragraph (1)(A), by adding after and below clause

(ii) the following:

‘In making the determination whether to approve or deny the application, the Secretary shall rely on the conditions of use included in the proposed labeling as the basis for determining whether or not there is a reasonable assurance of safety and effectiveness, if the proposed labeling is neither false nor misleading. In determining whether or not such labeling is false or misleading, the Secretary shall fairly evaluate all material facts pertinent to the proposed labeling.’; and

(2) by adding after paragraph (5) (as added by section 202(2)) the following:

‘(6) (A)(i) A supplemental application shall be required for any change to a device subject to an approved application under this subsection that affects safety or effectiveness, unless such change is a modification in a manufacturing procedure or method of manufacturing and the holder of the approved application submits a written notice to the Secretary that describes in detail the change, summarizes the data or information supporting the change, and informs the Secretary that the change has been made under the requirements of section 520(f).

‘(ii) The holder of an approved application who submits a notice under clause (i) with respect to a manufacturing change of a device may distribute the device 30 days after the date on which the Secretary receives the notice, unless the Secretary within such 30-day period notifies the holder that the notice is not adequate and describes such further information or action that is required for acceptance of such change. If the Secretary notifies the holder that a supplemental application is required, the Secretary shall review the supplement within 135 days after the receipt of the supplement. The time used by the Secretary to review the notice of the manufacturing change shall be deducted from the 135-day review period if the notice meets appropriate content requirements for premarket approval supplements.

‘(B) (i) Subject to clause (ii), in reviewing a supplement to an approved application, for an incremental change to the design of a device that affects safety or effectiveness, the Secretary shall approve such supplement if—

‘(I) nonclinical data demonstrate that the design modification creates the intended additional capacity, function, or performance of the device; and

‘(II) clinical data from the approved application and any supplement to the approved application provide a reason-

able assurance of safety and effectiveness for the changed device.

- ‘(ii) The Secretary may require, when necessary, additional clinical data to evaluate the design modification of the device to provide a reasonable assurance of safety and effectiveness.’.

SEC. 206. PREMARKET NOTIFICATION.

- (a) SECTION 510- Section 510 (21 U.S.C. 360) is amended—

(1) in subsection (k), in the matter preceding paragraph (1), by adding after ‘report to the Secretary’ the following: ‘or person who is accredited under section 523(a)’; and

(2) by adding at the end the following subsections:

- ‘(l) A report under subsection (k) is not required for a device intended for human use that is exempted from the requirements of this subsection under subsection (m) or is within a type that has been classified into class I under section 513. The exception established in the preceding sentence does not apply to any class I device that is intended for a use which is of substantial importance in preventing impairment of human health, or to any class I device that presents a potential unreasonable risk of illness or injury.

- ‘(m) (1) Not later than 60 days after the date of enactment of the Food and Drug Administration Modernization Act of 1997, the Secretary shall publish in the Federal Register a list of each type of class II device that does not require a report under subsection (k) to provide reasonable assurance of safety and effectiveness. Each type of class II device identified by the Secretary as not requiring the report shall be exempt from the requirement to provide a report under subsection (k) as of the date of the publication of the list in the Federal Register.

‘(2) Beginning on the date that is 1 day after the date of the publication of a list under this subsection, the Secretary may exempt a class II device from the requirement to submit a report under subsection (k), upon the Secretary’s own initiative or a petition of an interested person, if the Secretary determines that such report is not necessary to assure the safety and effectiveness of the device. The Secretary shall publish in the Federal Register notice of the intent of the Secretary to exempt the device, or of the petition, and provide a 30-day period for public comment. Within 120 days after the issuance of the notice in the Federal Register, the Secretary shall publish an order in the Federal Register that sets forth the final determination of the Secretary regarding the exemption of the device that was the subject of the notice. If the Secretary fails to respond to a petition within 180 days of receiving it, the petition shall be deemed to be granted.’.

- (b) SECTION 513(f)- Section 513(f) (21 U.S.C. 360c(f)) is amended by adding at the end the following:

‘(5) The Secretary may not withhold a determination of the initial classification of a device under paragraph (1) because of a failure to comply with

any provision of this Act unrelated to a substantial equivalence decision, including a finding that the facility in which the device is manufactured is not in compliance with good manufacturing requirements as set forth in regulations of the Secretary under section 520(f) (other than a finding that there is a substantial likelihood that the failure to comply with such regulations will potentially present a serious risk to human health).’.

(c) SECTION 513(i)- Section 513(i)(1) (21 U.S.C. 360c(i)), as amended by section 205(b), is amended—

(1) in subparagraph (A)(ii)—

(A) in subclause (I), by striking ‘clinical data’ and inserting ‘appropriate clinical or scientific data’ and by inserting ‘or a person accredited under section 523’ after ‘Secretary’; and

(B) in subclause (II), by striking ‘efficacy’ and inserting ‘effectiveness’; and

(2) by adding at the end the following:

‘(F) Not later than 270 days after the date of the enactment of the Food and Drug Administration Modernization Act of 1997, the Secretary shall issue guidance specifying the general principles that the Secretary will consider in determining when a specific intended use of a device is not reasonably included within a general use of such device for purposes of a determination of substantial equivalence under subsection (f) or section 520(1).’.

SEC. 207. EVALUATION OF AUTOMATIC CLASS III DESIGNATION.

Section 513(f) (21 U.S.C. 360c(f)), as amended by section 206(b), is amended—

(1) in paragraph (1)—

(A) in subparagraph (B), by striking ‘paragraph (2)’ and inserting ‘paragraph (3)’; and

(B) in the last sentence, by striking ‘paragraph (2)’ and inserting ‘paragraph (2) or (3)’;

(2) by redesignating paragraphs (2) and (3) as paragraphs (3) and (4), respectively; and

(3) by inserting after paragraph (1) the following:

‘(2) (A) Any person who submits a report under section 510(k) for a type of device that has not been previously classified under this Act, and that is classified into class III under paragraph (1), may request, within 30 days after receiving written notice of such a classification, the Secretary to classify the device under the criteria set forth in subparagraphs (A) through (C) of subsection (a)(1). The person may, in the request, recommend to the Secretary a classification for the device. Any such request shall describe the device and provide detailed information and reasons for the recommended classification.

‘(B) (i) Not later than 60 days after the date of the submission of the request under subparagraph (A), the Secretary shall by written order classify the device involved. Such classification shall be the initial classification of the device for purposes of paragraph (1) and any

device classified under this paragraph shall be a predicate device for determining substantial equivalence under paragraph (1).

‘(ii) A device that remains in class III under this subparagraph shall be deemed to be adulterated within the meaning of section 501(f)(1)(B) until approved under section 515 or exempted from such approval under section 520(g).

‘(C) Within 30 days after the issuance of an order classifying a device under this paragraph, the Secretary shall publish a notice in the Federal Register announcing such classification.’.

SEC. 208. CLASSIFICATION PANELS.

Section 513(b) (21 U.S.C. 360c(b)) is amended by adding at the end the following:

‘(5) Classification panels covering each type of device shall be scheduled to meet at such times as may be appropriate for the Secretary to meet applicable statutory deadlines.

‘(6) (A) Any person whose device is specifically the subject of review by a classification panel shall have—

‘(i) the same access to data and information submitted to a classification panel (except for data and information that are not available for public disclosure under section 552 of title 5, United States Code) as the Secretary;

‘(ii) the opportunity to submit, for review by a classification panel, information that is based on the data or information provided in the application submitted under section 515 by the person, which information shall be submitted to the Secretary for prompt transmittal to the classification panel; and

‘(iii) the same opportunity as the Secretary to participate in meetings of the panel.

‘(B) Any meetings of a classification panel shall provide adequate time for initial presentations and for response to any differing views by persons whose devices are specifically the subject of a classification panel review, and shall encourage free and open participation by all interested persons.

‘(7) After receiving from a classification panel the conclusions and recommendations of the panel on a matter that the panel has reviewed, the Secretary shall review the conclusions and recommendations, shall make a final decision on the matter in accordance with section 515(d)(2), and shall notify the affected persons of the decision in writing and, if the decision differs from the conclusions and recommendations of the panel, shall include the reasons for the difference.

‘(8) A classification panel under this subsection shall not be subject to the annual chartering and annual report requirements of the Federal Advisory Committee Act.’.

(a) CERTAINTY OF REVIEW TIMEFRAMES- Section 510 (21 U.S.C. 360), as

amended by section 206(a)(2), is amended by adding at the end the following subsection:

- ‘(n) The Secretary shall review the report required in subsection (k) and make a determination under section 513(f)(1) not later than 90 days after receiving the report.’.
- (b) COLLABORATIVE REVIEW PROCESS- Section 515(d) (21 U.S.C. 360e(d)), as amended by section 202(1), is amended by inserting after paragraph (2) the following:
 - ‘(3) (A)(i) The Secretary shall, upon the written request of an applicant, meet with the applicant, not later than 100 days after the receipt of an application that has been filed as complete under subsection (c), to discuss the review status of the application.
 - ‘(ii) The Secretary shall, in writing and prior to the meeting, provide to the applicant a description of any deficiencies in the application that, at that point, have been identified by the Secretary based on an interim review of the entire application and identify the information that is required to correct those deficiencies.
 - ‘(iii) The Secretary shall notify the applicant promptly of—
 - ‘(I) any additional deficiency identified in the application, or
 - ‘(II) any additional information required to achieve completion of the review and final action on the application, that was not described as a deficiency in the written description provided by the Secretary under clause (ii).
 - ‘(B) The Secretary and the applicant may, by mutual consent, establish a different schedule for a meeting required under this paragraph.
- (a) IN GENERAL- Subchapter A of chapter V is amended by adding at the end the following:

‘SEC. 523. ACCREDITED PERSONS.

- ‘(a) IN GENERAL—
 - ‘(1) REVIEW AND CLASSIFICATION OF DEVICES- Not later than 1 year after the date of the enactment of the Food and Drug Administration Modernization Act of 1997, the Secretary shall, subject to paragraph (3), accredit persons for the purpose of reviewing reports submitted under section 510(k) and making recommendations to the Secretary regarding the initial classification of devices under section 513(f)(1).
 - ‘(2) REQUIREMENTS REGARDING REVIEW-
 - ‘(A) IN GENERAL- In making a recommendation to the Secretary under paragraph (1), an accredited person shall notify the Secretary in writing of the reasons for the recommendation.
 - ‘(B) TIME PERIOD FOR REVIEW- Not later than 30 days after the date on which the Secretary is notified under subparagraph (A) by an accredited person with respect to a recommendation of an initial

classification of a device, the Secretary shall make a determination with respect to the initial classification.

‘(C) SPECIAL RULE- The Secretary may change the initial classification under section 513(f)(1) that is recommended under paragraph (1) by an accredited person, and in such case shall provide to such person, and the person who submitted the report under section 510(k) for the device, a statement explaining in detail the reasons for the change.

‘(3) CERTAIN DEVICES-

‘(A) IN GENERAL- An accredited person may not be used to perform a review of—

‘(i) a class III device;

‘(ii) a class II device which is intended to be permanently implantable or life sustaining or life supporting; or

‘(iii) a class II device which requires clinical data in the report submitted under section 510(k) for the device, except that the number of class II devices to which the Secretary applies this clause for a year, less the number of such reports to which clauses (i) and (ii) apply, may not exceed 6 percent of the number that is equal to the total number of reports submitted to the Secretary under such section for such year less the number of such reports to which such clauses apply for such year.

‘(B) ADJUSTMENT- In determining for a year the ratio described in subparagraph (A)(iii), the Secretary shall not include in the numerator class III devices that the Secretary reclassified into class II, and the Secretary shall include in the denominator class II devices for which reports under section 510(k) were not required to be submitted by reason of the operation of section 510(m).

‘(b) ACCREDITATION—

‘(1) PROGRAMS- The Secretary shall provide for such accreditation through programs administered by the Food and Drug Administration, other government agencies, or by other qualified nongovernment organizations.

‘(2) ACCREDITATION—

‘(A) IN GENERAL- Not later than 180 days after the date of the enactment of the Food and Drug Administration Modernization Act of 1997, the Secretary shall establish and publish in the Federal Register criteria to accredit or deny accreditation to persons who request to perform the duties specified in subsection (a). The Secretary shall respond to a request for accreditation within 60 days of the receipt of the request. The accreditation of such person shall specify the particular activities under subsection (a) for which such person is accredited.

‘(B) WITHDRAWAL OF ACCREDITATION- The Secretary may suspend or withdraw accreditation of any person accredited under this paragraph, after providing notice and an opportunity for an informal hearing, when such person is substantially not in compliance with

the requirements of this section or poses a threat to public health or fails to act in a manner that is consistent with the purposes of this section.

‘(C) PERFORMANCE AUDITING- To ensure that persons accredited under this section will continue to meet the standards of accreditation, the Secretary shall—

‘(i) make onsite visits on a periodic basis to each accredited person to audit the performance of such person; and

‘(ii) take such additional measures as the Secretary determines to be appropriate.

‘(D) ANNUAL REPORT- The Secretary shall include in the annual report required under section 903(g) the names of all accredited persons and the particular activities under subsection (a) for which each such person is accredited and the name of each accredited person whose accreditation has been withdrawn during the year.

‘(3) QUALIFICATIONS- An accredited person shall, at a minimum, meet the following requirements:

‘(A) Such person may not be an employee of the Federal Government.

‘(B) Such person shall be an independent organization which is not owned or controlled by a manufacturer, supplier, or vendor of devices and which has no organizational, material, or financial affiliation with such a manufacturer, supplier, or vendor.

‘(C) Such person shall be a legally constituted entity permitted to conduct the activities for which it seeks accreditation.

‘(D) Such person shall not engage in the design, manufacture, promotion, or sale of devices.

‘(E) The operations of such person shall be in accordance with generally accepted professional and ethical business practices and shall agree in writing that as a minimum it will—

‘(i) certify that reported information accurately reflects data reviewed;

‘(ii) limit work to that for which competence and capacity are available;

‘(iii) treat information received, records, reports, and recommendations as proprietary information;

‘(iv) promptly respond and attempt to resolve complaints regarding its activities for which it is accredited; and

‘(v) protect against the use, in carrying out subsection (a) with respect to a device, of any officer or employee of the person who has a financial conflict of interest regarding the device, and annually make available to the public disclosures of the extent to which the person, and the officers and employees of the person, have maintained compliance with requirements under this clause relating to financial conflicts of interest.

‘(4) SELECTION OF ACCREDITED PERSONS- The Secretary shall provide each person who chooses to use an accredited person to receive a

section 510(k) report a panel of at least two or more accredited persons from which the regulated person may select one for a specific regulatory function.

- ‘(5) COMPENSATION OF ACCREDITED PERSONS- Compensation for an accredited person shall be determined by agreement between the accredited person and the person who engages the services of the accredited person, and shall be paid by the person who engages such services.
- ‘(c) DURATION- The authority provided by this section terminates—
 - ‘(1) 5 years after the date on which the Secretary notifies Congress that at least 2 persons accredited under subsection (b) are available to review at least 60 percent of the submissions under section 510(k), or
 - ‘(2) 4 years after the date on which the Secretary notifies Congress that the Secretary has made a determination described in paragraph (2)(B) of subsection (a) for at least 35 percent of the devices that are subject to review under paragraph (1) of such subsection, whichever occurs first.’.
- (b) RECORDKEEPING- Section 704 (21 U.S.C. 374) is amended by adding at the end the following:
 - ‘(f) (1) A person accredited under section 523 to review reports made under section 510(k) and make recommendations of initial classifications of devices to the Secretary shall maintain records documenting the training qualifications of the person and the employees of the person, the procedures used by the person for handling confidential information, the compensation arrangements made by the person, and the procedures used by the person to identify and avoid conflicts of interest. Upon the request of an officer or employee designated by the Secretary, the person shall permit the officer or employee, at all reasonable times, to have access to, to copy, and to verify, the records.
 - ‘(2) Within 15 days after the receipt of a written request from the Secretary to a person accredited under section 523 for copies of records described in paragraph (1), the person shall produce the copies of the records at the place designated by the Secretary.’.
- (c) CONFORMING AMENDMENT- Section 301 (21 U.S.C. 331), as amended by section 204(b), is amended by adding at the end the following:
- ‘(y) In the case of a drug, device, or food—
 - ‘(1) the submission of a report or recommendation by a person accredited under section 523 that is false or misleading in any material respect;
 - ‘(2) the disclosure by a person accredited under section 523 of confidential commercial information or any trade secret without the express written consent of the person who submitted such information or secret to such person; or
 - ‘(3) the receipt by a person accredited under section 523 of a bribe in any form or the doing of any corrupt act by such person associated with a responsibility delegated to such person under this Act.’.
- (d) REPORTS ON PROGRAM OF ACCREDITATION-
 - (1) COMPTROLLER GENERAL-
 - (A) IMPLEMENTATION OF PROGRAM- Not later than 5 years after the date of the enactment of this Act, the Comptroller General of

the United States shall submit to the Committee on Commerce of the House of Representatives and the Committee on Labor and Human Resources of the Senate a report describing the extent to which the program of accreditation required by the amendment made by subsection (a) has been implemented.

- (B) EVALUATION OF PROGRAM- Not later than 6 months prior to the date on which, pursuant to subsection (c) of section 523 of the Federal Food, Drug and Cosmetic Act (as added by subsection (a)), the authority provided under subsection (a) of such section will terminate, the Comptroller General shall submit to the Committee on Commerce of the House of Representatives and the Committee on Labor and Human Resources of the Senate a report describing the use of accredited persons under such section 523, including an evaluation of the extent to which such use assisted the Secretary in carrying out the duties of the Secretary under such Act with respect to devices, and the extent to which such use promoted actions which are contrary to the purposes of such Act.
- (2) INCLUSION OF CERTAIN DEVICES WITHIN PROGRAM- Not later than 3 years after the date of the enactment of this Act, the Secretary of Health and Human Services shall submit to the Committee on Commerce of the House of Representatives and the Committee on Labor and Human Resources of the Senate a report providing a determination by the Secretary of whether, in the program of accreditation established pursuant to the amendment made by subsection (a), the limitation established in clause (iii) of section 523(a)(3)(A) of the Federal Food, Drug and Cosmetic Act (relating to class II devices for which clinical data are required in reports under section 510(k)) should be removed.

SEC. 211. DEVICE TRACKING.

Effective 90 days after the date of the enactment of this Act, section 519(e) (21 U.S.C. 360i(e)) is amended to read as follows:

‘DEVICE TRACKING

- ‘(e) (1) The Secretary may by order require a manufacturer to adopt a method of tracking a class II or class III device—
- ‘(A) the failure of which would be reasonably likely to have serious adverse health consequences; or
 - ‘(B) which is—
 - ‘(i) intended to be implanted in the human body for more than one year, or
 - ‘(ii) a life sustaining or life supporting device used outside a device user facility.
- ‘(2) Any patient receiving a device subject to tracking under paragraph (1) may refuse to release, or refuse permission to release, the patient’s name,

address, social security number, or other identifying information for the purpose of tracking.’.

SEC. 212. POSTMARKET SURVEILLANCE.

Effective 90 days after the date of the enactment of this Act, Section 522 (21 U.S.C. 3601) is amended to read as follows:.

‘POSTMARKET SURVEILLANCE

‘SEC. 522. (a) IN GENERAL- The Secretary may by order require a manufacturer to conduct postmarket surveillance for any device of the manufacturer which is a class II or class III device the failure of which would be reasonably likely to have serious adverse health consequences or which is intended to be—

‘(1) implanted in the human body for more than one year, or

‘(2) a life sustaining or life supporting device used outside a device user facility.

‘(b) SURVEILLANCE APPROVAL- Each manufacturer required to conduct a surveillance of a device shall, within 30 days of receiving an order from the Secretary prescribing that the manufacturer is required under this section to conduct such surveillance, submit, for the approval of the Secretary, a plan for the required surveillance. The Secretary, within 60 days of the receipt of such plan, shall determine if the person designated to conduct the surveillance has appropriate qualifications and experience to undertake such surveillance and if the plan will result in the collection of useful data that can reveal unforeseen adverse events or other information necessary to protect the public health. The Secretary, in consultation with the manufacturer, may by order require a prospective surveillance period of up to 36 months. Any determination by the Secretary that a longer period is necessary shall be made by mutual agreement between the Secretary and the manufacturer or, if no agreement can be reached, after the completion of a dispute resolution process as described in section 562.’.

SEC. 213. REPORTS.

(a) REPORTS- Section 519 (21 U.S.C. 360i) is amended—

(1) in subsection (a)—

(A) in the matter preceding paragraph (1), by striking ‘manufacturer, importer, or distributor’ and inserting ‘manufacturer or importer’;

(B) in paragraph (4), by striking ‘manufacturer, importer, or distributor’ and inserting ‘manufacturer or importer’;

(C) in paragraph (7), by adding ‘and’ after the semicolon at the end;

(D) in paragraph (8)—

(i) by striking ‘manufacturer, importer, or distributor’ each place such term appears and inserting ‘manufacturer or importer’; and

- (ii) by striking the semicolon at the end and inserting a period;
- (E) by striking paragraph (9); and
- (F) by inserting at the end the following sentence: ‘The Secretary shall by regulation require distributors to keep records and make such records available to the Secretary upon request. Paragraphs (4) and (8) apply to distributors to the same extent and in the same manner as such paragraphs apply to manufacturers and importers.’;
- (2) by striking subsection (d); and
- (3) in subsection (f), by striking, ‘importer, or distributor’ each place it appears and inserting ‘or importer’.
- (b) REGISTRATION- Section 510(g) (21 U.S.C. 360(g)) is amended—
 - (1) by redesignating paragraph (4) as paragraph (5);
 - (2) by inserting after paragraph (3) the following:
 - ‘(4) any distributor who acts as a wholesale distributor of devices, and who does not manufacture, repack, process, or relabel a device; or’; and
 - (3) by adding at the end the following flush sentence:

‘In this subsection, the term ‘wholesale distributor’ means any person (other than the manufacturer or the initial importer) who distributes a device from the original place of manufacture to the person who makes the final delivery or sale of the device to the ultimate consumer or user.’.

(c) DEVICE USER FACILITIES-

- (1) IN GENERAL- Section 519(b) (21 U.S.C. 360i(b)) is amended—
 - (A) in paragraph (1)(C)—
 - (i) in the first sentence, by striking ‘a semi-annual basis’ and inserting ‘an annual basis’;
 - (ii) in the second sentence, by striking ‘and July 1’; and
 - (iii) by striking the matter after and below clause (iv); and
 - (B) in paragraph (2)—
 - (i) in subparagraph (A), by inserting ‘or’ after the comma at the end;
 - (ii) in subparagraph (B), by striking ‘, or’ at the end and inserting a period; and
 - (iii) by striking subparagraph (C).
- (2) SENTINEL SYSTEM- Section 519(b) (21 U.S.C. 360i(b)) is amended—
 - (A) by redesignating paragraph (5) as paragraph (6); and
 - (B) by inserting after paragraph (4) the following paragraph:
 - ‘(5) With respect to device user facilities:
 - ‘(A) The Secretary shall by regulation plan and implement a program under which the Secretary limits user reporting under paragraphs (1) through (4) to a subset of user facilities that constitutes a representative profile of user reports for device deaths and serious illnesses or serious injuries.
 - ‘(B) During the period of planning the program under subparagraph (A), paragraphs (1) through (4) continue to apply.
 - ‘(C) During the period in which the Secretary is providing for a transition to the full implementation of the program, paragraphs (1) through

(4) apply except to the extent that the Secretary determines otherwise.

‘(D) On and after the date on which the program is fully implemented, paragraphs (1) through (4) do not apply to a user facility unless the facility is included in the subset referred to in subparagraph (A).

‘(E) Not later than 2 years after the date of the enactment of the Food and Drug Administration Modernization Act of 1997, the Secretary shall submit to the Committee on Commerce of the House of Representatives, and to the Committee on Labor and Human Resources of the Senate, a report describing the plan developed by the Secretary under subparagraph (A) and the progress that has been made toward the implementation of the plan.’.

SEC. 214. PRACTICE OF MEDICINE.

Chapter IX is amended by adding at the end the following:

‘SEC. 906. PRACTICE OF MEDICINE.

‘Nothing in this Act shall be construed to limit or interfere with the authority of a health care practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate health care practitioner-patient relationship. This section shall not limit any existing authority of the Secretary to establish and enforce restrictions on the sale or distribution, or in the labeling, of a device that are part of a determination of substantial equivalence, established as a condition of approval, or promulgated through regulations. Further, this section shall not change any existing prohibition on the promotion of unapproved uses of legally marketed devices.’.

SEC. 215. NONINVASIVE BLOOD GLUCOSE METER.

(a) FINDINGS- The Congress finds that—

- (1) diabetes and its complications are a leading cause of death by disease in America;
- (2) diabetes affects approximately 16,000,000 Americans and another 650,000 will be diagnosed in 1997;
- (3) the total health care-related costs of diabetes total nearly \$100,000,000,000 per year;
- (4) diabetes is a disease that is managed and controlled on a daily basis by the patient;
- (5) the failure to properly control and manage diabetes results in costly and often fatal complications including but not limited to blindness, coronary artery disease, and kidney failure;
- (6) blood testing devices are a critical tool for the control and management

- of diabetes, and existing blood testing devices require repeated piercing of the skin;
- (7) the pain associated with existing blood testing devices creates a disincentive for people with diabetes to test blood glucose levels, particularly children;
 - (8) a safe and effective noninvasive blood glucose meter would likely improve control and management of diabetes by increasing the number of tests conducted by people with diabetes, particularly children; and
 - (9) the Food and Drug Administration is responsible for reviewing all applications for new medical devices in the United States.
- (b) SENSE OF CONGRESS- It is the sense of the Congress that the availability of a safe, effective, noninvasive blood glucose meter would greatly enhance the health and well-being of all people with diabetes across America and the world.
- (a) USE OF DATA RELATING TO PREMARKET APPROVAL-
- (1) IN GENERAL- Section 520(h)(4) (21 U.S.C. 360j(h)(4)) is amended to read as follows:
 - “(4) (A) Any information contained in an application for premarket approval filed with the Secretary pursuant to section 515(c) (including information from clinical and preclinical tests or studies that demonstrate the safety and effectiveness of a device, but excluding descriptions of methods of manufacture and product composition and other trade secrets) shall be available, 6 years after the application has been approved by the Secretary, for use by the Secretary in—
 - “(i) approving another device;
 - “(ii) determining whether a product development protocol has been completed, under section 515 for another device;
 - “(iii) establishing a performance standard or special control under this Act; or
 - “(iv) classifying or reclassifying another device under section 513 and subsection (1)(2).
 - “(B) The publicly available detailed summaries of information respecting the safety and effectiveness of devices required by paragraph (1)(A) shall be available for use by the Secretary as the evidentiary basis for the agency actions described in subparagraph (A).”.
 - (2) CONFORMING AMENDMENTS- Section 517(a) (21 U.S.C. 360g(a)) is amended—
 - (A) in paragraph (8), by adding ‘or’ at the end;
 - (B) in paragraph (9), by striking ‘, or’ and inserting a comma; and
 - (C) by striking paragraph (10).
- (b) PRODUCT DEVELOPMENT PROTOCOL- Section 515(f)(2) (21 U.S.C. 360e(f)(2)) is amended by striking ‘he shall’ and all that follows and inserting the following: ‘the Secretary—
- “(A) may, at the initiative of the Secretary, refer the proposed protocol to the appropriate panel under section 513 for its recommendation respecting approval of the protocol; or

‘(B) shall so refer such protocol upon the request of the submitter, unless the Secretary finds that the proposed protocol and accompanying data which would be reviewed by such panel substantially duplicate a product development protocol and accompanying data which have previously been reviewed by such a panel.’.

Section 513(a)(3)(A) (21 U.S.C. 360c(a)(3)(A)) is amended by striking ‘clinical investigations’ and inserting ‘1 or more clinical investigations’.

TITLE III—IMPROVING REGULATION OF FOOD

SEC. 301. FLEXIBILITY FOR REGULATIONS REGARDING CLAIMS.

Section 403(r) (21 U.S.C. 343(r)) is amended by adding at the end the following:

- ‘(7) The Secretary may make proposed regulations issued under this paragraph effective upon publication pending consideration of public comment and publication of a final regulation if the Secretary determines that such action is necessary—
 - ‘(A) to enable the Secretary to review and act promptly on petitions the Secretary determines provide for information necessary to—
 - ‘(i) enable consumers to develop and maintain healthy dietary practices;
 - ‘(ii) enable consumers to be informed promptly and effectively of important new knowledge regarding nutritional and health benefits of food; or
 - ‘(iii) ensure that scientifically sound nutritional and health information is provided to consumers as soon as possible; or
 - ‘(B) to enable the Secretary to act promptly to ban or modify a claim under this paragraph.

Such proposed regulations shall be deemed final agency action for purposes of judicial review.’.

SEC. 302. PETITIONS FOR CLAIMS.

Section 403(r)(4)(A)(i) (21 U.S.C. 343(r)(4)(A)(i)) is amended—

- (1) by adding after the second sentence the following: ‘If the Secretary does not act within such 100 days, the petition shall be deemed to be denied unless an extension is mutually agreed upon by the Secretary and the petitioner.’;
- (2) in the fourth sentence (as amended by paragraph (1)) by inserting immediately before the comma the following: ‘or the petition is deemed to be denied’; and
- (3) by adding at the end the following: ‘If the Secretary does not act within such 90 days, the petition shall be deemed to be denied unless an extension is mutually agreed upon by the Secretary and the petitioner. If the Secretary issues a proposed regulation, the rulemaking shall be completed

within 540 days of the date the petition is received by the Secretary. If the Secretary does not issue a regulation within such 540 days, the Secretary shall provide the Committee on Commerce of the House of Representatives and the Committee on Labor and Human Resources of the Senate the reasons action on the regulation did not occur within such 540 days.’.

SEC. 303. HEALTH CLAIMS FOR FOOD PRODUCTS.

Section 403(r)(3) (21 U.S.C. 343(r)(3)) is amended by adding at the end thereof the following:

- (C) Notwithstanding the provisions of clauses (A)(i) and (B), a claim of the type described in subparagraph (1)(B) which is not authorized by the Secretary in a regulation promulgated in accordance with clause (B) shall be authorized and may be made with respect to a food if—
 - ‘(i) a scientific body of the United States Government with official responsibility for public health protection or research directly relating to human nutrition (such as the National Institutes of Health or the Centers for Disease Control and Prevention) or the National Academy of Sciences or any of its subdivisions has published an authoritative statement, which is currently in effect, about the relationship between a nutrient and a disease or health-related condition to which the claim refers;
 - ‘(ii) a person has submitted to the Secretary, at least 120 days (during which the Secretary may notify any person who is making a claim as authorized by clause (C) that such person has not submitted all the information required by such clause) before the first introduction into interstate commerce of the food with a label containing the claim, (I) a notice of the claim, which shall include the exact words used in the claim and shall include a concise description of the basis upon which such person relied for determining that the requirements of subclause (i) have been satisfied, (II) a copy of the statement referred to in subclause (i) upon which such person relied in making the claim, and (III) a balanced representation of the scientific literature relating to the relationship between a nutrient and a disease or health-related condition to which the claim refers;
 - ‘(iii) the claim and the food for which the claim is made are in compliance with clause (A)(ii) and are otherwise in compliance with paragraph (a) and section 201(n); and
 - ‘(iv) the claim is stated in a manner so that the claim is an accurate representation of the authoritative statement referred to in

subclause (i) and so that the claim enables the public to comprehend the information provided in the claim and to understand the relative significance of such information in the context of a total daily diet.

For purposes of this clause, a statement shall be regarded as an authoritative statement of a scientific body described in subclause (i) only if the statement is published by the scientific body and shall not include a statement of an employee of the scientific body made in the individual capacity of the employee.

‘(D) A claim submitted under the requirements of clause (C) may be made until—

‘(i) such time as the Secretary issues a regulation under the standard in clause (B)(i)—

‘(I) prohibiting or modifying the claim and the regulation has become effective, or

‘(II) finding that the requirements of clause (C) have not been met, including finding that the petitioner has not submitted all the information required by such clause; or

‘(ii) a district court of the United States in an enforcement proceeding under chapter III has determined that the requirements of clause (C) have not been met.’.

SEC. 304. NUTRIENT CONTENT CLAIMS.

Section 403(r)(2) (21 U.S.C. 343(r)(2)) is amended by adding at the end the following:

‘(G) A claim of the type described in subparagraph (1)(A) for a nutrient, for which the Secretary has not promulgated a regulation under clause (A)(i), shall be authorized and may be made with respect to a food if—

‘(i) a scientific body of the United States Government with official responsibility for public health protection or research directly relating to human nutrition (such as the National Institutes of Health or the Centers for Disease Control and Prevention) or the National Academy of Sciences or any of its subdivisions has published an authoritative statement, which is currently in effect, which identifies the nutrient level to which the claim refers;

‘(ii) a person has submitted to the Secretary, at least 120 days (during which the Secretary may notify any person who is making a claim as authorized by clause (C) that such person has not submitted all the information required by such clause) before the first introduction into interstate commerce of the food with a label containing the claim, (I) a notice of the claim, which shall include the exact words used in the claim and shall include a concise description of the basis upon which such person relied for determining that the requirements of subclause

(i) have been satisfied, (II) a copy of the statement referred to in subclause (i) upon which such person relied in making the claim, and (III) a balanced representation of the scientific literature relating to the nutrient level to which the claim refers;

‘(iii) the claim and the food for which the claim is made are in compliance with clauses (A) and (B), and are otherwise in compliance with paragraph (a) and section 201 (n); and

‘(iv) the claim is stated in a manner so that the claim is an accurate representation of the authoritative statement referred to in subclause (i) and so that the claim enables the public to comprehend the information provided in the claim and to understand the relative significance of such information in the context of a total daily diet.

For purposes of this clause, a statement shall be regarded as an authoritative statement of a scientific body described in subclause (i) only if the statement is published by the scientific body and shall not include a statement of an employee of the scientific body made in the individual capacity of the employee.

‘(H) A claim submitted under the requirements of clause (G) may be made until—

‘(i) such time as the Secretary issues a regulation—

‘(I) prohibiting or modifying the claim and the regulation has become effective, or

‘(II) finding that the requirements of clause (G) have not been met, including finding that the petitioner had not submitted all the information required by such clause; or

‘(ii) a district court of the United States in an enforcement proceeding under chapter III has determined that the requirements of clause (G) have not been met.’.

SEC. 305. REFERRAL STATEMENTS.

Section 403(r)(2) (B) (21 U.S.C. 343(r)(2)(B)) is amended to read as follows:

‘(B) If a claim described in subparagraph (1)(A) is made with respect to a nutrient in a food and the Secretary makes a determination that the food contains a nutrient at a level that increases to persons in the general population the risk of a disease or health-related condition that is diet related, the label or labeling of such food shall contain, prominently and in immediate proximity to such claim, the following statement: ‘See nutrition information for [Bold-> XX] [<-Bold] content.’ The blank shall identify the nutrient associated with the increased disease or health-related condition risk. In making the determination described in this clause, the Secretary shall take into account the significance of the food in the total daily diet.’.

SEC. 306. DISCLOSURE OF IRRADIATION.

Chapter IV (21 U.S.C. 341 et seq.) is amended by inserting after section 403B the following:

‘DISCLOSURE

‘SEC. 403C. (a) No provision of section 201(n), 403(a), or 409 shall be construed to require on the label or labeling of a food a separate radiation disclosure statement that is more prominent than the declaration of ingredients required by section 403(i)(2).

‘(b) In this section, the term ‘radiation disclosure statement’ means a written statement that discloses that a food has been intentionally subject to radiation.’.

SEC. 307. IRRADIATION PETITION.

Not later than 60 days following the date of the enactment of this Act, the Secretary of Health and Human Services shall make a final determination on any petition pending with the Food and Drug Administration that would permit the irradiation of red meat under section 409(b)(1) of the Federal Food, Drug and Cosmetic Act. If the Secretary does not make such determination, the Secretary shall, not later than 60 days following the date of the enactment of this Act, provide the Committee on Commerce of the House of Representatives and the Committee on Labor and Human Resources of the Senate an explanation of the process followed by the Food and Drug Administration in reviewing the petition referred to in paragraph (1) and the reasons action on the petition was delayed.

SEC. 308. GLASS AND CERAMIC WARE.

- (a) IN GENERAL—The Secretary may not implement any requirement which would ban, as an unapproved food additive, lead and cadmium based enamel in the lip and rim area of glass and ceramic ware before the expiration of one year after the date such requirement is published.
- (b) LEAD AND CADMIUM BASED ENAMEL—Unless the Secretary determines, based on available data, that lead and cadmium based enamel on glass and ceramic ware—
 - (1) which has less than 60 millimeters of decorating area below the external rim, and
 - (2) which is not, by design, representation, or custom of usage intended for use by children, is unsafe, the Secretary shall not take any action before January 1, 2003, to ban lead and cadmium based enamel on such glass and ceramic ware. Any action taken after January 1, 2003, to ban such enamel on such glass and ceramic ware as an unapproved food additive shall be taken by regulation and such regulation shall provide that such products shall not be removed from the market before 1 year after publication of the final regulation.

SEC. 309. FOOD CONTACT SUBSTANCES.

- (a) FOOD CONTACT SUBSTANCES—Section 409(a) (21 U.S.C. 348(a)) is amended—

- (1) in paragraph (1)—
 - (A) by striking ‘subsection (i)’ and inserting ‘subsection (j)’; and
 - (B) by striking at the end ‘or’;
- (2) by striking the period at the end of paragraph (2) and inserting ‘; or’;
- (3) by inserting after paragraph (2) the following:
- ‘(3) in the case of a food additive as defined in this Act that is a food contact substance, there is—
 - ‘(A) in effect, and such substance and the use of such substance are in conformity with, a regulation issued under this section prescribing the conditions under which such additive may be safely used; or
 - ‘(B) a notification submitted under subsection (h) that is effective.’; and
- (4) by striking the matter following paragraph (3) (as added by paragraph (3)) and inserting the following flush sentence: ‘While such a regulation relating to a food additive, or such a notification under subsection (h)(1) relating to a food additive that is a food contact substance, is in effect, and has not been revoked pursuant to subsection (i), a food shall not, by reason of bearing or containing such a food additive in accordance with the regulation or notification, be considered adulterated under section 402(a)(1).’.
- (b) NOTIFICATION FOR FOOD CONTACT SUBSTANCES—Section 409 (21 U.S.C. 348), as amended by subsection (a), is further amended—
 - (1) by redesignating subsections (h) and (i), as subsections (i) and (j), respectively;
 - (2) by inserting after subsection (g) the following:

‘NOTIFICATION RELATING TO A FOOD CONTACT SUBSTANCE

- ‘(h) (1) Subject to such regulations as may be promulgated under paragraph (3), a manufacturer or supplier of a food contact substance may, at least 120 days prior to the introduction or delivery for introduction into interstate commerce of the food contact substance, notify the Secretary of the identity and intended use of the food contact substance, and of the determination of the manufacturer or supplier that the intended use of such food contact substance is safe under the standard described in subsection (c)(3)(A). The notification shall contain the information that forms the basis of the determination and all information required to be submitted by regulations promulgated by the Secretary.
- ‘(2) (A) A notification submitted under paragraph (1) shall become effective 120 days after the date of receipt by the Secretary and the food contact substance may be introduced or delivered for introduction into interstate commerce, unless the Secretary makes a determination within the 120-day period that, based on the data and information before the Secretary, such use of the food contact substance has not been shown to be safe under the standard described in subsection (c)(3)(A), and informs the manufacturer or supplier of such determination.
- ‘(B) A decision by the Secretary to object to a notification shall constitute final agency action subject to judicial review.

- ‘(C) In this paragraph, the term ‘food contact substance’ means the substance that is the subject of a notification submitted under paragraph (1), and does not include a similar or identical substance manufactured or prepared by a person other than the manufacturer identified in the notification.
- ‘(3) (A) The process in this subsection shall be utilized for authorizing the marketing of a food contact substance except where the Secretary determines that submission and review of a petition under subsection (b) is necessary to provide adequate assurance of safety, or where the Secretary and any manufacturer or supplier agree that such manufacturer or supplier may submit a petition under subsection (b).
- ‘(B) The Secretary is authorized to promulgate regulations to identify the circumstances in which a petition shall be filed under subsection (b), and shall consider criteria such as the probable consumption of such food contact substance and potential toxicity of the food contact substance in determining the circumstances in which a petition shall be filed under subsection (b).
- ‘(4) The Secretary shall keep confidential any information provided in a notification under paragraph (1) for 120 days after receipt by the Secretary of the notification. After the expiration of such 120 days, the information shall be available to any interested party except for any matter in the notification that is a trade secret or confidential commercial information.
- ‘(5) (A)(i) Except as provided in clause (ii), the notification program established under this subsection shall not operate in any fiscal year unless—
 - ‘(I) an appropriation equal to or exceeding the applicable amount under clause (iv) is made for such fiscal year for carrying out such program in such fiscal year; and
 - ‘(II) the Secretary certifies that the amount appropriated for such fiscal year for the Center for Food Safety and Applied Nutrition of the Food and Drug Administration (exclusive of the appropriation referred to in subclause (I)) equals or exceeds the amount appropriated for the Center for fiscal year 1997, excluding any amount appropriated for new programs.
- ‘(ii) The Secretary shall, not later than April 1, 1999, begin accepting and reviewing notifications submitted under the notification program established under this subsection if—
 - ‘(I) an appropriation equal to or exceeding the applicable amount under clause (iii) is made for the last six months of fiscal year 1999 for carrying out such program during such period; and
 - ‘(II) the Secretary certifies that the amount appropriated for such period for the Center for Food Safety and Applied Nutrition of the Food and Drug Administration (exclusive of the appropriation referred to in subclause (I))

equals or exceeds an amount equivalent to one-half the amount appropriated for the Center for fiscal year 1997, excluding any amount appropriated for new programs.

- ‘(iii) For the last six months of fiscal year 1999, the applicable amount under this clause is \$1,500,000, or the amount specified in the budget request of the President for the six-month period involved for carrying out the notification program in fiscal year 1999, whichever is less.
- ‘(iv) For fiscal year 2000 and subsequent fiscal years, the applicable amount under this clause is \$3,000,000, or the amount specified in the budget request of the President for the fiscal year involved for carrying out the notification program under this subsection, whichever is less.
- ‘(B) For purposes of carrying out the notification program under this subsection, there are authorized to be appropriated such sums as may be necessary for each of the fiscal years 1999 through fiscal year 2003, except that such authorization of appropriations is not effective for a fiscal year for any amount that is less than the applicable amount under clause (iii) or (iv) of subparagraph (A), whichever is applicable.
- ‘(C) Not later than April 1 of fiscal year 1998 and February 1 of each subsequent fiscal year, the Secretary shall submit a report to the Committees on Appropriations of the House of Representatives and the Senate, the Committee on Commerce of the House of Representatives, and the Committee on Labor and Human Resources of the Senate that provides an estimate of the Secretary of the costs of carrying out the notification program established under this subsection for the next fiscal year.
- ‘(6) In this section, the term ‘food contact substance’ means any substance intended for use as a component of materials used in manufacturing, packing, packaging, transporting, or holding food if such use is not intended to have any technical effect in such food.’;
- (3) in subsection (i), as so redesignated by paragraph (1), by adding at the end the following: ‘The Secretary shall by regulation prescribe the procedure by which the Secretary may deem a notification under subsection (h) to no longer be effective.’; and
- (4) in subsection (j), as so redesignated by paragraph (1), by striking ‘subsections (b) to (h)’ and inserting ‘subsections (b) to (i)’.

TITLE IV—GENERAL PROVISIONS

SEC. 401. DISSEMINATION OF INFORMATION ON NEW USES.

- (a) IN GENERAL- Chapter V (21 U.S.C. 351 et seq.) is amended by inserting after subchapter C the following:

‘SUBCHAPTER D—DISSEMINATION OF TREATMENT
INFORMATION

‘SEC. 551. REQUIREMENTS FOR DISSEMINATION OF TREATMENT
INFORMATION ON DRUGS OR DEVICES.

- ‘(a) IN GENERAL- Notwithstanding sections 301(d), 502(f), and 505, and section 351 of the Public Health Service Act (42 U.S.C. 262), a manufacturer may disseminate to—
 - ‘(1) a health care practitioner;
 - ‘(2) a pharmacy benefit manager;
 - ‘(3) a health insurance issuer;
 - ‘(4) a group health plan; or
 - ‘(5) a Federal or State governmental agency; written information concerning the safety, effectiveness, or benefit of a use not described in the approved labeling of a drug or device if the manufacturer meets the requirements of subsection (b).
- ‘(b) SPECIFIC REQUIREMENTS- A manufacturer may disseminate information under subsection (a) on a new use only if—
 - ‘(1) (A) in the case of a drug, there is in effect for the drug an application filed under subsection (b) or (j) of section 505 or a biologics license issued under section 351 of the Public Health Service Act; or
 - ‘(B) in the case of a device, the device is being commercially distributed in accordance with a regulation under subsection (d) or (e) of section 513, an order under subsection (f) of such section, or the approval of an application under section 515;
 - ‘(2) the information meets the requirements of section 552;
 - ‘(3) the information to be disseminated is not derived from clinical research conducted by another manufacturer or if it was derived from research conducted by another manufacturer, the manufacturer disseminating the information has the permission of such other manufacturer to make the dissemination;
 - ‘(4) the manufacturer has, 60 days before such dissemination, submitted to the Secretary—
 - ‘(A) a copy of the information to be disseminated; and
 - ‘(B) any clinical trial information the manufacturer has relating to the safety or effectiveness of the new use, any reports of clinical experience pertinent to the safety of the new use, and a summary of such information;
 - ‘(5) the manufacturer has complied with the requirements of section 554 (relating to a supplemental application for such use);
 - ‘(6) the manufacturer includes along with the information to be disseminated under this subsection—
 - ‘(A) a prominently displayed statement that discloses—

- ‘(i) that the information concerns a use of a drug or device that has not been approved or cleared by the Food and Drug Administration;
 - ‘(ii) if applicable, that the information is being disseminated at the expense of the manufacturer;
 - ‘(iii) if applicable, the name of any authors of the information who are employees of, consultants to, or have received compensation from, the manufacturer, or who have a significant financial interest in the manufacturer;
 - ‘(iv) the official labeling for the drug or device and all updates with respect to the labeling;
 - ‘(v) if applicable, a statement that there are products or treatments that have been approved or cleared for the use that is the subject of the information being disseminated pursuant to subsection (a)(1); and
 - ‘(vi) the identification of any person that has provided funding for the conduct of a study relating to the new use of a drug or device for which such information is being disseminated; and
- ‘(B) a bibliography of other articles from a scientific reference publication or scientific or medical journal that have been previously published about the use of the drug or device covered by the information disseminated (unless the information already includes such bibliography).
- ‘(c) ADDITIONAL INFORMATION- If the Secretary determines, after providing notice of such determination and an opportunity for a meeting with respect to such determination, that the information submitted by a manufacturer under subsection (b)(3)(B), with respect to the use of a drug or device for which the manufacturer intends to disseminate information, fails to provide data, analyses, or other written matter that is objective and balanced, the Secretary may require the manufacturer to disseminate—
- ‘(1) additional objective and scientifically sound information that pertains to the safety or effectiveness of the use and is necessary to provide objectivity and balance, including any information that the manufacturer has submitted to the Secretary or, where appropriate, a summary of such information or any other information that the Secretary has authority to make available to the public; and
 - ‘(2) an objective statement of the Secretary, based on data or other scientifically sound information available to the Secretary, that bears on the safety or effectiveness of the new use of the drug or device.

‘SEC. 552. INFORMATION AUTHORIZED TO BE DISSEMINATED.

- ‘(a) AUTHORIZED INFORMATION- A manufacturer may disseminate information under section 551 on a new use only if the information—
- ‘(1) is in the form of an unabridged—

- ‘(A) reprint or copy of an article, peer-reviewed by experts qualified by scientific training or experience to evaluate the safety or effectiveness of the drug or device involved, which was published in a scientific or medical journal (as defined in section 556(5)), which is about a clinical investigation with respect to the drug or device, and which would be considered to be scientifically sound by such experts; or
- ‘(B) reference publication, described in subsection (b), that includes information about a clinical investigation with respect to the drug or device that would be considered to be scientifically sound by experts qualified by scientific training or experience to evaluate the safety or effectiveness of the drug or device that is the subject of such a clinical investigation; and
- ‘(2) is not false or misleading and would not pose a significant risk to the public health.
- ‘(b) REFERENCE PUBLICATION- A reference publication referred to in subsection (a)(1)(B) is a publication that—
 - ‘(1) has not been written, edited, excerpted, or published specifically for, or at the request of, a manufacturer of a drug or device;
 - ‘(2) has not been edited or significantly influenced by such a manufacturer;
 - ‘(3) is not solely distributed through such a manufacturer but is generally available in bookstores or other distribution channels where medical textbooks are sold;
 - ‘(4) does not focus on any particular drug or device of a manufacturer that disseminates information under section 551 and does not have a primary focus on new uses of drugs or devices that are marketed or under investigation by a manufacturer supporting the dissemination of information; and
 - ‘(5) presents materials that are not false or misleading.

‘SEC. 553. ESTABLISHMENT OF LIST OF ARTICLES AND PUBLICATIONS DISSEMINATED AND LIST OF PROVIDERS THAT RECEIVED ARTICLES AND REFERENCE PUBLICATIONS.

- ‘(a) IN GENERAL- A manufacturer may disseminate information under section 551 on a new use only if the manufacturer prepares and submits to the Secretary biannually—
 - ‘(1) a list containing the titles of the articles and reference publications relating to the new use of drugs or devices that were disseminated by the manufacturer to a person described in section 551(a) for the 6-month period preceding the date on which the manufacturer submits the list to the Secretary; and
 - ‘(2) a list that identifies the categories of providers (as described in section 551(a)) that received the articles and reference publications for the 6-month period described in paragraph (1).
- ‘(b) RECORDS- A manufacturer that disseminates information under section 551 shall keep records that may be used by the manufacturer when, pursuant to section 555, such manufacturer is required to take corrective action and shall

be made available to the Secretary, upon request, for purposes of ensuring or taking corrective action pursuant to such section. Such records, at the Secretary's discretion, may identify the recipient of information provided pursuant to section 551 or the categories of such recipients.

**'SEC. 554. REQUIREMENT REGARDING SUBMISSION OF
SUPPLEMENTAL APPLICATION FOR NEW USE; EXEMPTION
FROM REQUIREMENT.**

- '(a) IN GENERAL- A manufacturer may disseminate information under section 551 on a new use only if—
 - '(1) (A) the manufacturer has submitted to the Secretary a supplemental application for such use; or
 - '(B) the manufacturer meets the condition described in subsection (b) or (c) (relating to a certification that the manufacturer will submit such an application); or
 - '(2) there is in effect for the manufacturer an exemption under subsection (d) from the requirement of paragraph (1).
- '(b) CERTIFICATION ON SUPPLEMENTAL APPLICATION; CONDITION IN CASE OF COMPLETED STUDIES- For purposes of subsection (a)(1)(B), a manufacturer may disseminate information on a new use if the manufacturer has submitted to the Secretary an application containing a certification that—
 - '(1) the studies needed for the submission of a supplemental application for the new use have been completed; and
 - '(2) the supplemental application will be submitted to the Secretary not later than 6 months after the date of the initial dissemination of information under section 551.
- '(c) CERTIFICATION ON SUPPLEMENTAL APPLICATION; CONDITION IN CASE OF PLANNED STUDIES—
 - '(1) IN GENERAL- For purposes of subsection (a)(1)(B), a manufacturer may disseminate information on a new use if—
 - '(A) the manufacturer has submitted to the Secretary an application containing—
 - '(i) a proposed protocol and schedule for conducting the studies needed for the submission of a supplemental application for the new use; and
 - '(ii) a certification that the supplemental application will be submitted to the Secretary not later than 36 months after the date of the initial dissemination of information under section 551 (or, as applicable, not later than such date as the Secretary may specify pursuant to an extension under paragraph (3)); and
 - '(B) the Secretary has determined that the proposed protocol is adequate and that the schedule for completing such studies is reasonable.
 - '(2) PROGRESS REPORTS ON STUDIES- A manufacturer that submits to

the Secretary an application under paragraph (1) shall submit to the Secretary periodic reports describing the status of the studies involved.

‘(3) EXTENSION OF TIME REGARDING PLANNED STUDIES- The period of 36 months authorized in paragraph (1)(A)(ii) for the completion of studies may be extended by the Secretary if—

‘(A) the Secretary determines that the studies needed to submit such an application cannot be completed and submitted within 36 months; or

‘(B) the manufacturer involved submits to the Secretary a written request for the extension and the Secretary determines that the manufacturer has acted with due diligence to conduct the studies in a timely manner, except that an extension under this subparagraph may not be provided for more than 24 additional months.

‘(d) EXEMPTION FROM REQUIREMENT OF SUPPLEMENTAL APPLICATION—

‘(1) IN GENERAL- For purposes of subsection (a)(2), a manufacturer may disseminate information on a new use if—

‘(A) the manufacturer has submitted to the Secretary an application for an exemption from meeting the requirement of subsection (a)(1); and

‘(B) (i) the Secretary has approved the application in accordance with paragraph (2); or

‘(ii) the application is deemed under paragraph (3)(A) to have been approved (unless such approval is terminated pursuant to paragraph (3)(B)).

‘(2) CONDITIONS FOR APPROVAL- The Secretary may approve an application under paragraph (1) for an exemption if the Secretary makes a determination described in subparagraph (A) or (B), as follows:

‘(A) The Secretary makes a determination that, for reasons defined by the Secretary, it would be economically prohibitive with respect to such drug or device for the manufacturer to incur the costs necessary for the submission of a supplemental application. In making such determination, the Secretary shall consider (in addition to any other considerations the Secretary finds appropriate)—

‘(i) the lack of the availability under law of any period during which the manufacturer would have exclusive marketing rights with respect to the new use involved; and

‘(ii) the size of the population expected to benefit from approval of the supplemental application.

‘(B) The Secretary makes a determination that, for reasons defined by the Secretary, it would be unethical to conduct the studies necessary for the supplemental application. In making such determination, the Secretary shall consider (in addition to any other considerations the Secretary finds appropriate) whether the new use involved is the standard of medical care for a health condition.

‘(3) TIME FOR CONSIDERATION OF APPLICATION; DEEMED APPROVAL—

- ‘(A) IN GENERAL- The Secretary shall approve or deny an application under paragraph (1) for an exemption not later than 60 days after the receipt of the application. If the Secretary does not comply with the preceding sentence, the application is deemed to be approved.
- ‘(B) TERMINATION OF DEEMED APPROVAL- If pursuant to a deemed approval under subparagraph (A) a manufacturer disseminates written information under section 551 on a new use, the Secretary may at any time terminate such approval and under section 555(b)(3) order the manufacturer to cease disseminating the information.
- ‘(e) REQUIREMENTS REGARDING APPLICATIONS- Applications under this section shall be submitted in the form and manner prescribed by the Secretary.

‘SEC. 555. CORRECTIVE ACTIONS; CESSATION OF DISSEMINATION.

- ‘(a) POSTDISSEMINATION DATA REGARDING SAFETY AND EFFECTIVENESS-
 - ‘(1) CORRECTIVE ACTIONS- With respect to data received by the Secretary after the dissemination of information under section 551 by a manufacturer has begun (whether received pursuant to paragraph (2) or otherwise), if the Secretary determines that the data indicate that the new use involved may not be effective or may present a significant risk to public health, the Secretary shall, after consultation with the manufacturer, take such action regarding the dissemination of the information as the Secretary determines to be appropriate for the protection of the public health, which may include ordering that the manufacturer cease the dissemination of the information.
 - ‘(2) RESPONSIBILITIES OF MANUFACTURERS TO SUBMIT DATA- After a manufacturer disseminates information under section 551, the manufacturer shall submit to the Secretary a notification of any additional knowledge of the manufacturer on clinical research or other data that relate to the safety or effectiveness of the new use involved. If the manufacturer is in possession of the data, the notification shall include the data. The Secretary shall by regulation establish the scope of the responsibilities of manufacturers under this paragraph, including such limits on the responsibilities as the Secretary determines to be appropriate.
- ‘(b) CESSATION OF DISSEMINATION-
 - ‘(1) FAILURE OF MANUFACTURER TO COMPLY WITH REQUIREMENTS- The Secretary may order a manufacturer to cease the dissemination of information pursuant to section 551 if the Secretary determines that the information being disseminated does not comply with the requirements established in this subchapter. Such an order may be issued only after the Secretary has provided notice to the manufacturer of the intent of the Secretary to issue the order and (unless paragraph (2) (B) applies)

has provided an opportunity for a meeting with respect to such intent. If the failure of the manufacturer constitutes a minor violation of this subchapter, the Secretary shall delay issuing the order and provide to the manufacturer an opportunity to correct the violation.

‘(2) SUPPLEMENTAL APPLICATIONS- The Secretary may order a manufacturer to cease the dissemination of information pursuant to section 551 if—

‘(A) in the case of a manufacturer that has submitted a supplemental application for a new use pursuant to section 554 (a) (1), the Secretary determines that the supplemental application does not contain adequate information for approval of the new use for which the application was submitted;

‘(B) in the case of a manufacturer that has submitted a certification under section 554 (b), the manufacturer has not, within the 6-month period involved, submitted the supplemental application referred to in the certification; or

‘(C) in the case of a manufacturer that has submitted a certification under section 554 (c) but has not yet submitted the supplemental application referred to in the certification, the Secretary determines, after an informal hearing, that the manufacturer is not acting with due diligence to complete the studies involved.

‘(3) TERMINATION OF DEEMED APPROVAL OF EXEMPTION REGARDING SUPPLEMENTAL APPLICATION- If under section 554 (d) (3) the Secretary terminates a deemed approval of an exemption, the Secretary may order the manufacturer involved to cease disseminating the information. A manufacturer shall comply with an order under the preceding sentence not later than 60 days after the receipt of the order.

‘(c) CORRECTIVE ACTIONS BY MANUFACTURERS-

‘(1) IN GENERAL- In any case in which under this section the Secretary orders a manufacturer to cease disseminating information, the Secretary may order the manufacturer to take action to correct the information that has been disseminated, except as provided in paragraph (2).

‘(2) TERMINATION OF DEEMED APPROVAL OF EXEMPTION REGARDING SUPPLEMENTAL APPLICATIONS- In the case of an order under subsection (b) (3) to cease disseminating information, the Secretary may not order the manufacturer involved to take action to correct the information that has been disseminated unless the Secretary determines that the new use described in the information would pose a significant risk to the public health.

‘SEC. 556. DEFINITIONS.

‘For purposes of this subchapter:

‘(1) The term ‘health care practitioner’ means a physician, or other individual

who is a provider of health care, who is licensed under the law of a State to prescribe drugs or devices.

- ‘(2) The terms ‘health insurance issuer’ and ‘group health plan’ have the meaning given such terms under section 2791 of the Public Health Service Act.
- ‘(3) The term ‘manufacturer’ means a person who manufactures a drug or device, or who is licensed by such person to distribute or market the drug or device.
- ‘(4) The term ‘new use’—
 - ‘(A) with respect to a drug, means a use that is not included in the labeling of the approved drug; and
 - ‘(B) with respect to a device, means a use that is not included in the labeling for the approved or cleared device.
- ‘(5) The term ‘scientific or medical journal’ means a scientific or medical publication—
 - ‘(A) that is published by an organization—
 - ‘(i) that has an editorial board;
 - ‘(ii) that utilizes experts, who have demonstrated expertise in the subject of an article under review by the organization and who are independent of the organization, to review and objectively select, reject, or provide comments about proposed articles; and
 - ‘(iii) that has a publicly stated policy, to which the organization adheres, of full disclosure of any conflict of interest or biases for all authors or contributors involved with the journal or organization;
 - ‘(B) whose articles are peer-reviewed and published in accordance with the regular peer-review procedures of the organization;
 - ‘(C) that is generally recognized to be of national scope and reputation;
 - ‘(D) that is indexed in the Index Medicus of the National Library of Medicine of the National Institutes of Health; and
 - ‘(E) that is not in the form of a special supplement that has been funded in whole or in part by one or more manufacturers.

‘SEC. 557. RULES OF CONSTRUCTION.

- ‘(a) UNSOLICITED REQUEST- Nothing in section 551 shall be construed as prohibiting a manufacturer from disseminating information in response to an unsolicited request from a health care practitioner.
- ‘(b) DISSEMINATION OF INFORMATION ON DRUGS OR DEVICES NOT EVIDENCE OF INTENDED USE- Notwithstanding subsection (a), (f), or (o) of section 502, or any other provision of law, the dissemination of information relating to a new use of a drug or device, in accordance with section 551, shall not be construed by the Secretary as evidence of a new intended use of the drug or device that is different from the intended use of the drug or device set forth in the official labeling of the drug or device. Such dissemination shall

not be considered by the Secretary as labeling, adulteration, or misbranding of the drug or device.

- ‘(c) PATENT PROTECTION- Nothing in section 551 shall affect patent rights in any manner.
- ‘(d) AUTHORIZATION FOR DISSEMINATION OF ARTICLES AND FEES FOR REPRINTS OF ARTICLES- Nothing in section 551 shall be construed as prohibiting an entity that publishes a scientific journal (as defined in section 556(5)) from requiring authorization from the entity to disseminate an article published by such entity or charging fees for the purchase of reprints of published articles from such entity.’.
- (b) PROHIBITED ACT- Section 301 (21 U.S.C. 331), as amended by section 210, is amended by adding at the end the following:
- ‘(z) The dissemination of information in violation of section 551.’.
- (c) REGULATIONS- Not later than 1 year after the date of enactment of this Act, the Secretary of Health and Human Services shall promulgate regulations to implement the amendments made by this section.
- (d) EFFECTIVE DATE- The amendments made by this section shall take effect 1 year after the date of enactment of this Act, or upon the Secretary’s issuance of final regulations pursuant to subsection (c), whichever is sooner.
- (e) SUNSET- The amendments made by this section cease to be effective September 30, 2006, or 7 years after the date on which the Secretary promulgates the regulations described in subsection (c), whichever is later.
- (f) STUDIES AND REPORTS-
 - (1) GENERAL ACCOUNTING OFFICE-
 - (A) IN GENERAL- The Comptroller General of the United States shall conduct a study to determine the impact of subchapter D of chapter V of the Federal Food, Drug and Cosmetic Act, as added by this section, on the resources of the Department of Health and Human Services.
 - (B) REPORT- Not later than January 1, 2002, the Comptroller General of the United States shall prepare and submit to the Committee on Labor and Human Resources of the Senate and the Committee on Commerce of the House of Representatives a report of the results of the study.
 - (2) DEPARTMENT OF HEALTH AND HUMAN SERVICES-
 - (A) IN GENERAL- In order to assist Congress in determining whether the provisions of such subchapter should be extended beyond the termination date specified in subsection (e), the Secretary of Health and Human Services shall, in accordance with subparagraph (B), arrange for the conduct of a study of the scientific issues raised as a result of the enactment of such subchapter including issues relating to—
 - (i) the effectiveness of such subchapter with respect to the provision of useful scientific information to health care practitioners;
 - (ii) the quality of the information being disseminated pursuant to the provisions of such subchapter;

- (iii) the quality and usefulness of the information provided, in accordance with such subchapter, by the Secretary or by the manufacturer at the request of the Secretary; and
 - (iv) the impact of such subchapter on research in the area of new uses, indications, or dosages, particularly the impact on pediatric indications and rare diseases.
- (3) PROCEDURE FOR STUDY-

(A) IN GENERAL- The Secretary shall request the Institute of Medicine of the National Academy of Sciences to conduct the study required by paragraph (2), and to prepare and submit the report required by subparagraph (B), under an arrangement by which the actual expenses incurred by the Institute of Medicine in conducting the study and preparing the report will be paid by the Secretary. If the Institute of Medicine is unwilling to conduct the study under such an arrangement, the Comptroller General of the United States shall conduct such study.

(B) REPORT- Not later than September 30, 2005, the Institute of Medicine or the Comptroller General of the United States, as appropriate, shall prepare and submit to the Committee on Labor and Human Resources of the Senate, the Committee on Commerce of the House of Representatives, and the Secretary a report of the results of the study required by paragraph (2). The Secretary, after the receipt of the report, shall make the report available to the public.

Chapter V (21 U.S.C. 351 et seq.), as amended in section 401, is further amended by adding at the end the following:

‘SUBCHAPTER E—GENERAL PROVISIONS RELATING TO DRUGS AND DEVICES

‘SEC. 561. EXPANDED ACCESS TO UNAPPROVED THERAPIES AND DIAGNOSTICS.

- ‘(a) EMERGENCY SITUATIONS- The Secretary may, under appropriate conditions determined by the Secretary, authorize the shipment of investigational drugs or investigational devices for the diagnosis, monitoring, or treatment of a serious disease or condition in emergency situations.
- ‘(b) INDIVIDUAL PATIENT ACCESS TO INVESTIGATIONAL PRODUCTS INTENDED FOR SERIOUS DISEASES- Any person, acting through a physician licensed in accordance with State law, may request from a manufacturer or distributor, and any manufacturer or distributor may, after complying with the provisions of this subsection, provide to such physician an investigational drug or investigational device for the diagnosis, monitoring, or treatment of a serious disease or condition if—

- ‘(1) the licensed physician determines that the person has no comparable or satisfactory alternative therapy available to diagnose, monitor, or treat the disease or condition involved, and that the probable risk to the person from the investigational drug or investigational device is not greater than the probable risk from the disease or condition;
 - ‘(2) the Secretary determines that there is sufficient evidence of safety and effectiveness to support the use of the investigational drug or investigational device in the case described in paragraph (1);
 - ‘(3) the Secretary determines that provision of the investigational drug or investigational device will not interfere with the initiation, conduct, or completion of clinical investigations to support marketing approval; and
 - ‘(4) the sponsor, or clinical investigator, of the investigational drug or investigational device submits to the Secretary a clinical protocol consistent with the provisions of section 505(i) or 520(g), including any regulations promulgated under section 505(i) or 520(g), describing the use of the investigational drug or investigational device in a single patient or a small group of patients.
- ‘(c) TREATMENT INVESTIGATIONAL NEW DRUG APPLICATIONS AND TREATMENT INVESTIGATIONAL DEVICE EXEMPTIONS- Upon submission by a sponsor or a physician of a protocol intended to provide widespread access to an investigational drug or investigational device for eligible patients (referred to in this subsection as an ‘expanded access protocol’), the Secretary shall permit such investigational drug or investigational device to be made available for expanded access under a treatment investigational new drug application or treatment investigational device exemption if the Secretary determines that—
- ‘(1) under the treatment investigational new drug application or treatment investigational device exemption, the investigational drug or investigational device is intended for use in the diagnosis, monitoring, or treatment of a serious or immediately life-threatening disease or condition;
 - ‘(2) there is no comparable or satisfactory alternative therapy available to diagnose, monitor, or treat that stage of disease or condition in the population of patients to which the investigational drug or investigational device is intended to be administered;
 - ‘(3) (A) the investigational drug or investigational device is under investigation in a controlled clinical trial for the use described in paragraph (1) under an investigational drug application in effect under section 505(i) or investigational device exemption in effect under section 520(g); or
 - ‘(B) all clinical trials necessary for approval of that use of the investigational drug or investigational device have been completed;
 - ‘(4) the sponsor of the controlled clinical trials is actively pursuing marketing approval of the investigational drug or investigational device for the use described in paragraph (1) with due diligence;

- ‘(5) in the case of an investigational drug or investigational device described in paragraph (3) (A), the provision of the investigational drug or investigational device will not interfere with the enrollment of patients in ongoing clinical investigations under section 505(i) or 520(g);
- ‘(6) in the case of serious diseases, there is sufficient evidence of safety and effectiveness to support the use described in paragraph (1); and
- ‘(7) in the case of immediately life-threatening diseases, the available scientific evidence, taken as a whole, provides a reasonable basis to conclude that the investigational drug or investigational device may be effective for its intended use and would not expose patients to an unreasonable and significant risk of illness or injury.

A protocol submitted under this subsection shall be subject to the provisions of section 505(i) or 520(g), including regulations promulgated under section 505(i) or 520(g). The secretary may inform national, State, and local medical associations and societies, voluntary health associations, and other appropriate persons about the availability of an investigational drug or investigational device under expanded access protocols submitted under this subsection. The information provided by the Secretary, in accordance with the preceding sentence, shall be the same type of information that is required by section 402 (j) (3) of the Public Health Service Act.

- ‘(d) TERMINATION- The Secretary may, at any time, with respect to a sponsor, physician, manufacturer, or distributor described in this section, terminate expanded access provided under this section for an investigational drug or investigational device if the requirements under this section are no longer met.
- ‘(e) DEFINITIONS- In this section, the terms ‘investigational drug’, ‘investigational device’, ‘treatment investigational new drug application’, and ‘treatment investigational device exemption’ shall have the meanings given the terms in regulations prescribed by the Secretary.’.
- (a) STANDARDS- Not later than 180 days after the date of enactment of this Act, the Secretary of Health and Human Services shall publish in the Federal Register standards for the prompt review of supplemental applications submitted for approved articles under the Federal Food, Drug and Cosmetic Act (21 U.S.C. 301 et seq.) or section 351 of the Public Health Service Act (42 U.S.C. 262).
- (b) GUIDANCE TO INDUSTRY—Not later than 180 days after the date of enactment of this Act, the Secretary shall issue final guidances to clarify the requirements for, and facilitate the submission of data to support, the approval of supplemental applications for the approved articles described in subsection (a). The guidances shall—
 - (1) clarify circumstances in which published matter may be the basis for approval of a supplemental application;
 - (2) specify data requirements that will avoid duplication of previously submitted data by recognizing the availability of data previously submitted in support of an original application; and
 - (3) define supplemental applications that are eligible for priority review.

- (c) RESPONSIBILITIES OF CENTERS- The Secretary shall designate an individual in each center within the Food and Drug Administration (except the Center for Food Safety and Applied Nutrition) to be responsible for—
 - (1) encouraging the prompt review of supplemental applications for approved articles; and
 - (2) working with sponsors to facilitate the development and submission of data to support supplemental applications.
- (d) COLLABORATION- The Secretary shall implement programs and policies that will foster collaboration between the Food and Drug Administration, the National Institutes of Health, professional medical and scientific societies, and other persons, to identify published and unpublished studies that may support a supplemental application, and to encourage sponsors to make supplemental applications or conduct further research in support of a supplemental application based, in whole or in part, on such studies.

SEC. 404. DISPUTE RESOLUTION.

Subchapter E of chapter V, as added by section 402, is amended by adding at the end the following:

‘SEC. 562. DISPUTE RESOLUTION.

‘If, regarding an obligation concerning drugs or devices under this Act or section 351 of the Public Health Service Act, there is a scientific controversy between the Secretary and a person who is a sponsor, applicant, or manufacturer and no specific provision of the Act involved, including a regulation promulgated under such Act, provides a right of review of the matter in controversy, the Secretary shall, by regulation, establish a procedure under which such sponsor, applicant, or manufacturer may request a review of such controversy, including a review by an appropriate scientific advisory panel described in section 505 (n) or an advisory committee described in section 515 (g) (2) (B). Any such review shall take place in a timely manner. The Secretary shall promulgate such regulations within 1 year after the date of the enactment of the Food and Drug Administration Modernization Act of 1997.’.

SEC. 405. INFORMAL AGENCY STATEMENTS.

Section 701 (21 U.S.C. 371) is amended by adding at the end the following:

- ‘(h) (1) (A) The Secretary shall develop guidance documents with public participation and ensure that information identifying the existence of such documents and the documents themselves are made available to the public both in written form and, as feasible, through electronic means. Such documents shall not create or confer any rights for or on any person, although they present the views of the Secretary on matters under the jurisdiction of the Food and Drug Administration.

- ‘(B) Although guidance documents shall not be binding on the Secretary, the Secretary shall ensure that employees of the Food and Drug Administration do not deviate from such guidances without appropriate justification and supervisory concurrence. The Secretary shall provide training to employees in how to develop and use guidance documents and shall monitor the development and issuance of such documents.
- ‘(C) For guidance documents that set forth initial interpretations of a statute or regulation, changes in interpretation or policy that are of more than a minor nature, complex scientific issues, or highly controversial issues, the Secretary shall ensure public participation prior to implementation of guidance documents, unless the Secretary determines that such prior public participation is not feasible or appropriate. In such cases, the Secretary shall provide for public comment upon implementation and take such comment into account.
- ‘(D) For guidance documents that set forth existing practices or minor changes in policy, the Secretary shall provide for public comment upon implementation.
- ‘(2) In developing guidance documents, the Secretary shall ensure uniform nomenclature for such documents and uniform internal procedures for approval of such documents. The Secretary shall ensure that guidance documents and revisions of such documents are properly dated and indicate the nonbinding nature of the documents. The Secretary shall periodically review all guidance documents and, where appropriate, revise such documents.
- ‘(3) The Secretary, acting through the Commissioner, shall maintain electronically and update and publish periodically in the Federal Register a list of guidance documents. All such documents shall be made available to the public.
- ‘(4) The Secretary shall ensure that an effective appeals mechanism is in place to address complaints that the Food and Drug Administration is not developing and using guidance documents in accordance with this subsection.
- ‘(5) Not later than July 1, 2000, the Secretary after evaluating the effectiveness of the Good Guidance Practices document, published in the Federal Register at 62 Fed. Reg. 8961, shall promulgate a regulation consistent with this subsection specifying the policies and procedures of the Food and Drug Administration for the development, issuance, and use of guidance documents.’
- (a) MISSION- Section 903 (21 U.S.C. 393) is amended—
 - (1) by redesignating subsections (b) and (c) as subsections (d) and (e), respectively; and
 - (2) by inserting after subsection (a) the following:
- ‘(b) MISSION- The Administration shall—
 - ‘(1) promote the public health by promptly and efficiently reviewing clinical

- research and taking appropriate action on the marketing of regulated products in a timely manner;
- ‘(2) with respect to such products, protect the public health by ensuring that—
 - ‘(A) foods are safe, wholesome, sanitary, and properly labeled;
 - ‘(B) human and veterinary drugs are safe and effective;
 - ‘(C) there is reasonable assurance of the safety and effectiveness of devices intended for human use;
 - ‘(D) cosmetics are safe and properly labeled; and
 - ‘(E) public health and safety are protected from electronic product radiation;
 - ‘(3) participate through appropriate processes with representatives of other countries to reduce the burden of regulation, harmonize regulatory requirements, and achieve appropriate reciprocal arrangements; and
 - ‘(4) as determined to be appropriate by the Secretary, carry out paragraphs (1) through (3) in consultation with experts in science, medicine, and public health, and in cooperation with consumers, users, manufacturers, importers, packers, distributors, and retailers of regulated products.’.
- (b) ANNUAL REPORT- Section 903 (21 U.S.C. 393), as amended by subsection (a), is further amended by adding at the end the following:
- ‘(f) AGENCY PLAN FOR STATUTORY COMPLIANCE-
- ‘(1) IN GENERAL- Not later than 1 year after the date of enactment of the Food and Drug Administration Modernization Act of 1997, the Secretary, after consultation with appropriate scientific and academic experts, health care professionals, representatives of patient and consumer advocacy groups, and the regulated industry, shall develop and publish in the Federal Register a plan bringing the Secretary into compliance with each of the obligations of the Secretary under this Act. The Secretary shall review the plan biannually and shall revise the plan as necessary, in consultation with such persons.
 - ‘(2) OBJECTIVES OF AGENCY PLAN- The plan required by paragraph (1) shall establish objectives and mechanisms to achieve such objectives, including objectives related to—
 - ‘(A) maximizing the availability and clarity of information about the process for review of applications and submissions (including petitions, notifications, and any other similar forms of request) made under this Act;
 - ‘(B) maximizing the availability and clarity of information for consumers and patients concerning new products;
 - ‘(C) implementing inspection and postmarket monitoring provisions of this Act;
 - ‘(D) ensuring access to the scientific and technical expertise needed by the Secretary to meet obligations described in paragraph (1);
 - ‘(E) establishing mechanisms, by July 1, 1999, for meeting the time periods specified in this Act for the review of all applications and submissions described in subparagraph (A) and submitted after the

date of enactment of the Food and Drug Administration Modernization Act of 1997; and

‘(F) eliminating backlogs in the review of applications and submissions described in subparagraph (A), by January 1, 2000.

‘(g) ANNUAL REPORT- The Secretary shall annually prepare and publish in the Federal Register and solicit public comment on a report that—

‘(1) provides detailed statistical information on the performance of the Secretary under the plan described in subsection (f);

‘(2) compares such performance of the Secretary with the objectives of the plan and with the statutory obligations of the Secretary; and

‘(3) identifies any regulatory policy that has a significant negative impact on compliance with any objective of the plan or any statutory obligation and sets forth any proposed revision to any such regulatory policy.’.

SEC. 407. INFORMATION SYSTEM.

(a) AMENDMENT- Chapter VII (21 U.S.C. 371 et seq.) is amended by adding at the end the following:

‘SUBCHAPTER D—INFORMATION AND EDUCATION

‘SEC. 741. INFORMATION SYSTEM.

‘The Secretary shall establish and maintain an information system to track the status and progress of each application or submission (including a petition, notification, or other similar form of request) submitted to the Food and Drug Administration requesting agency action.’.

(b) REPORT- Not later than 1 year after the date of enactment of this Act, the Secretary of Health and Human Services shall submit a report to the Committee on Labor and Human Resources of the Senate and the Committee on Commerce of the House of Representatives on the status of the system to be established under the amendment made by subsection (a), including the projected costs of the system and concerns about confidentiality.

SEC. 408. EDUCATION AND TRAINING.

(a) FOOD AND DRUG ADMINISTRATION- Chapter VII (21 U.S.C. 371 et seq.), as amended by section 407, is further amended by adding at the end the following section:.

‘SEC. 742. EDUCATION.

‘(a) IN GENERAL- The Secretary shall conduct training and education programs for the employees of the Food and Drug Administration relating to the regulatory responsibilities and policies established by this Act, including programs for—

- ‘(1) scientific training;
- ‘(2) training to improve the skill of officers and employees authorized to conduct inspections under section 704;
- ‘(3) training to achieve product specialization in such inspections; and
- ‘(4) training in administrative process and procedure and integrity issues.
- ‘(b) INTRAMURAL FELLOWSHIPS AND OTHER TRAINING PROGRAMS- The Secretary, acting through the Commissioner, may, through fellowships and other training programs, conduct and support intramural research training for predoctoral and postdoctoral scientists and physicians.’
- ‘(b) CENTERS FOR DISEASE CONTROL AND PREVENTION-
 - (1) IN GENERAL- Part B of title III of the Public Health Service Act is amended by inserting after section 317F (42 U.S.C. 247b-7) the following:

‘SEC. 317G. FELLOWSHIP AND TRAINING PROGRAMS.

‘The Secretary, acting through the Director of the Centers for Disease Control and Prevention, shall establish fellowship and training programs to be conducted by such Centers to train individuals to develop skills in epidemiology, surveillance, laboratory analysis, and other disease detection and prevention methods. Such programs shall be designed to enable health professionals and health personnel trained under such programs to work, after receiving such training, in local, State, national, and international efforts toward the prevention and control of diseases, injuries, and disabilities. Such fellowships and training may be administered through the use of either appointment or nonappointment procedures.’

- (2) EFFECTIVE DATE-The amendment made by this subsection is deemed to have taken effect July 1, 1995.

SEC. 409. CENTERS FOR EDUCATION AND RESEARCH ON THERAPEUTICS.

Title IX of the Public Health Service Act (42 U.S.C. 299 et seq.) is amended by adding at the end of part A the following new section:

SEC. 905. DEMONSTRATION PROGRAM REGARDING CENTERS FOR EDUCATION AND RESEARCH ON THERAPEUTICS.

- ‘(a) IN GENERAL- The Secretary, acting through the Administrator and in consultation with the Commissioner of Food and Drugs, shall establish a demonstration program for the purpose of making one or more grants for the establishment and operation of one or more centers to carry out the activities specified in subsection (b).
- ‘(b) REQUIRED ACTIVITIES- The activities referred to in subsection (a) are the following:

- ‘(1) The conduct of state-of-the-art clinical and laboratory research for the following purposes:
 - ‘(A) To increase awareness of—
 - ‘(i) new uses of drugs, biological products, and devices;
 - ‘(ii) ways to improve the effective use of drugs, biological products, and devices; and
 - ‘(iii) risks of new uses and risks of combinations of drugs and biological products.
 - ‘(B) To provide objective clinical information to the following individuals and entities:
 - ‘(i) Health care practitioners or other providers of health care goods or services.
 - ‘(ii) Pharmacy benefit managers.
 - ‘(iii) Health maintenance organizations or other managed health care organizations.
 - ‘(iv) Health care insurers or governmental agencies.
 - ‘(v) Consumers.
 - ‘(C) To improve the quality of health care while reducing the cost of health care through—
 - ‘(i) the appropriate use of drugs, biological products, or devices; and
 - ‘(ii) the prevention of adverse effects of drugs, biological products, and devices and the consequences of such effects, such as unnecessary hospitalizations.
- ‘(2) The conduct of research on the comparative effectiveness and safety of drugs, biological products, and devices.
 - ‘(3) Such other activities as the Secretary determines to be appropriate, except that the grant may not be expended to assist the Secretary in the review of new drugs.
- ‘(c) APPLICATION FOR GRANT-A grant under subsection (a) may be made only if an application for the grant is submitted to the Secretary and the application is in such form, is made in such manner, and contains such agreements, assurances, and information as the Secretary determines to be necessary to carry out this section.
- ‘(d) PEER REVIEW- A grant under subsection (a) may be made only if the application for the grant has undergone appropriate technical and scientific peer review.
- ‘(e) AUTHORIZATION OF APPROPRIATIONS- For the purpose of carrying out this section, there are authorized to be appropriated \$2,000,000 for fiscal year 1998, and \$3,000,000 for each of fiscal years 1999 through 2002.’.
- (a) GOOD MANUFACTURING PRACTICE REQUIREMENTS- Section 520 (f) (1) (B) (21 U.S.C. 360j (f) (1) (B)) is amended—
 - (1) in clause (i), by striking ‘, and’ at the end and inserting a semicolon;
 - (2) in clause (ii), by striking the period and inserting ‘; and’; and
 - (3) by inserting after clause (ii) the following:
 - ‘(iii) ensure that such regulation conforms, to the extent practica-

ble, with internationally recognized standards defining quality systems, or parts of the standards, for medical devices.’.

- ‘(b) HARMONIZATION EFFORTS- Section 803 (21 U.S.C. 383) is amended by adding at the end the following:
- ‘(c) (1) The Secretary shall support the Office of the United States Trade Representative, in consultation with the Secretary of Commerce, in meetings with representatives of other countries to discuss methods and approaches to reduce the burden of regulation and harmonize regulatory requirements if the Secretary determines that such harmonization continues consumer protections consistent with the purposes of this Act.
- ‘(2) The Secretary shall support the Office of the United States Trade Representative, in consultation with the Secretary of Commerce, in efforts to move toward the acceptance of mutual recognition agreements relating to the regulation of drugs, biological products, devices, foods, food additives, and color additives, and the regulation of good manufacturing practices, between the European Union and the United States.
- ‘(3) The Secretary shall regularly participate in meetings with representatives of other foreign governments to discuss and reach agreement on methods and approaches to harmonize regulatory requirements.
- ‘(4) The Secretary shall, not later than 180 days after the date of enactment of the Food and Drug Administration Modernization Act of 1997, make public a plan that establishes a framework for achieving mutual recognition of good manufacturing practices inspections.
- ‘(5) Paragraphs (1) through (4) shall not apply with respect to products defined in section 201 (ff).’.

SEC. 411. ENVIRONMENTAL IMPACT REVIEW.

Chapter VII (21 U.S.C. 371 et seq.), as amended by section 407, is further amended by adding at the end the following:

‘SUBCHAPTER E—ENVIRONMENTAL IMPACT REVIEW

‘SEC. 746. ENVIRONMENTAL IMPACT.

‘Notwithstanding any other provision of law, an environmental impact statement prepared in accordance with the regulations published in part 25 of title 21, Code of Federal Regulations (as in effect on August 31, 1997) in connection with an action carried out under (or a recommendation or report relating to) this Act, shall be considered to meet the requirements for a detailed statement under section 102 (2) (C) of the National Environmental Policy Act of 1969 (42 U.S.C. 4332 (2) (C)).’.

- (a) NONPRESCRIPTION DRUGS- Chapter VII (21 U.S.C. 371 et seq.), as amended by section 411, is further amended by adding at the end the following:

‘SUBCHAPTER F—NATIONAL UNIFORMITY FOR
NONPRESCRIPTION DRUGS AND PREEMPTION FOR
LABELING OR PACKAGING OF COSMETICS

‘SEC. 751. NATIONAL UNIFORMITY FOR NONPRESCRIPTION
DRUGS.

- ‘(a) IN GENERAL- Except as provided in subsection (b), (c) (1), (d), (e), or (f), no State or political subdivision of a State may establish or continue in effect any requirement—
 - ‘(1) that relates to the regulation of a drug that is not subject to the requirements of section 503 (b) (1) or 503 (f) (1) (A); and
 - ‘(2) that is different from or in addition to, or that is otherwise not identical with, a requirement under this Act, the Poison Prevention Packaging Act of 1970 (15 U.S.C. 1471 et seq.), or the Fair Packaging and Labeling Act (15 U.S.C. 1451 et seq.).
- ‘(b) EXEMPTION-
 - ‘(1) IN GENERAL- Upon application of a State or political subdivision thereof, the Secretary may by regulation, after notice and opportunity for written and oral presentation of views, exempt from subsection (a), under such conditions as may be prescribed in such regulation, a State or political subdivision requirement that—
 - ‘(A) protects an important public interest that would otherwise be unprotected, including the health and safety of children;
 - ‘(B) would not cause any drug to be in violation of any applicable requirement or prohibition under Federal law; and
 - ‘(C) would not unduly burden interstate commerce.
 - ‘(2) TIMELY ACTION- The Secretary shall make a decision on the exemption of a State or political subdivision requirement under paragraph (1) not later than 120 days after receiving the application of the State or political subdivision under paragraph (1).
- ‘(c) SCOPE-
 - ‘(1) IN GENERAL- This section shall not apply to —
 - ‘(A) any State or political subdivision requirement that relates to the practice of pharmacy; or
 - ‘(B) any State or political subdivision requirement that a drug be dispensed only upon the prescription of a practitioner licensed by law to administer such drug.
 - ‘(2) SAFETY OR EFFECTIVENESS- For purposes of subsection (a), a requirement that relates to the regulation of a drug shall be deemed to include any requirement relating to public information or any other form of public communication relating to a warning of any kind for a drug.
- ‘(d) EXCEPTIONS-
 - ‘(1) IN GENERAL- In the case of a drug described in subsection (a) (1) that

is not the subject of an application approved under section 505 or section 507 (as in effect on the day before the date of enactment of the Food and Drug Administration Modernization Act of 1997) or a final regulation promulgated by the Secretary establishing conditions under which the drug is generally recognized as safe and effective and not misbranded, subsection (a) shall apply only with respect to a requirement of a State or political subdivision of a State that relates to the same subject as, but is different from or in addition to, or that is otherwise not identical with—

‘(A) a regulation in effect with respect to the drug pursuant to a statute described in subsection (a) (2); or

‘(B) any other requirement in effect with respect to the drug pursuant to an amendment to such a statute made on or after the date of enactment of the Food and Drug Administration Modernization Act of 1997.

‘(2) STATE INITIATIVES- This section shall not apply to a State requirement adopted by a State public initiative or referendum enacted prior to September 1, 1997.

‘(e) NO EFFECT ON PRODUCT LIABILITY LAW- Nothing in this section shall be construed to modify or otherwise affect any action or the liability of any person under the product liability law of any State.

‘(f) STATE ENFORCEMENT AUTHORITY- Nothing in this section shall prevent a State or political subdivision thereof from enforcing, under any relevant civil or other enforcement authority, a requirement that is identical to a requirement of this Act.’.

(b) INSPECTIONS- Section 704 (a) (1) (21 U.S.C. 374 (a) (1)) is amended by striking ‘prescription drugs’ each place it appears and inserting ‘prescription drugs, nonprescription drugs intended for human use,’.

(c) MISBRANDING- Subparagraph (1) of section 502(e) (21 U.S.C. 352 (e) (1)) is amended to read as follows:

‘(1) (A) If it is a drug, unless its label bears, to the exclusion of any other nonproprietary name (except the applicable systematic chemical name or the chemical formula)—

‘(i) the established name (as defined in subparagraph (3)) of the drug, if there is such a name;

‘(ii) the established name and quantity or, if determined to be appropriate by the Secretary, the proportion of each active ingredient, including the quantity, kind, and proportion of any alcohol, and also including whether active or not the established name and quantity or if determined to be appropriate by the Secretary, the proportion of any bromides, ether, chloroform, acetanilide, acetophenetidin, amidopyrine, antipyrine, atropine, hyoscyne, hyoscyamine, arsenic, digitalis, digitalis glucosides, mercury, ouabain, strophanthin, strychnine, thyroid, or any derivative or preparation of any such substances, contained therein, except that the requirement for stating the

quantity of the active ingredients, other than the quantity of those specifically named in this subclause, shall not apply to nonprescription drugs not intended for human use; and

‘(iii) the established name of each inactive ingredient listed in alphabetical order on the outside container of the retail package and, if determined to be appropriate by the Secretary, on the immediate container, as prescribed in regulation promulgated by the Secretary, except that nothing in this subclause shall be deemed to require that any trade secret be divulged, and except that the requirements of this subclause with respect to alphabetical order shall apply only to nonprescription drugs that are not also cosmetics and that this subclause shall not apply to nonprescription drugs not intended for human use.

‘(B) For any prescription drug the established name of such drug or ingredient, as the case may be, on such label (and on any labeling on which a name for such drug or ingredient is used) shall be printed prominently and in type at least half as large as that used thereon for any proprietary name or designation for such drug or ingredient, except that to the extent that compliance with the requirements of subclause (ii) or (iii) of clause (A) or this clause is impracticable, exemptions shall be established by regulations promulgated by the Secretary.’

(d) COSMETICS- Subchapter F of chapter VII, as amended by subsection (a), is further amended by adding at the end the following:.

‘SEC. 752. PREEMPTION FOR LABELING OR PACKAGING OF COSMETICS.

‘(a) IN GENERAL- Except as provided in subsection (b), (d), or (e), no State or political subdivision of a State may establish or continue in effect any requirement for labeling or packaging of a cosmetic that is different from or in addition to, or that is otherwise not identical with, a requirement specifically applicable to a particular cosmetic or class of cosmetics under this Act, the Poison Prevention Packaging Act of 1970 (15 U.S.C. 1471 et seq.), or the Fair Packaging and Labeling Act (15 U.S.C. 1451 et seq.).

‘(b) EXEMPTION- Upon application of a State or political subdivision thereof, the Secretary may be regulation, after notice and opportunity for written and oral presentation of views, exempt from subsection (a), under such conditions as may be prescribed in such regulation, a State or political subdivision requirement for labeling or packaging that—

‘(1) protects an important public interest that would otherwise be unprotected;

‘(2) would not cause a cosmetic to be in violation of any applicable requirement or prohibition under Federal law; and

‘(3) would not unduly burden interstate commerce.

‘(c) SCOPE- For purposes of subsection (a), a reference to a State requirement that relates to the packaging or labeling of a cosmetic means any specific re-

quirement relating to the same aspect of such cosmetic as a requirement specifically applicable to that particular cosmetic or class of cosmetics under this Act for packaging or labeling, including any State requirement relating to public information or any other form of public communication.

- ‘(d) NO EFFECT ON PRODUCT LIABILITY LAW- Nothing in this section shall be construed to modify or otherwise affect any action or the liability of any person under the product liability law of any State.
- ‘(e) STATE INITIATIVE- This section shall not apply to a State requirement adopted by a State public initiative or referendum enacted prior to September 1, 1997.’.
- (a) LIST AND ANALYSIS- The Secretary of Health and Human Services shall, acting through the Food and Drug Administration—
 - (1) compile a list of drugs and foods that contain intentionally introduced mercury compounds, and
 - (2) provide a quantitative and qualitative analysis of the mercury compounds in the list under paragraph (1).

The Secretary shall compile the list required by paragraph (1) within 2 years after the date of enactment of the Food and Drug Administration Modernization Act of 1997 and shall provide the analysis required by paragraph (2) within 2 years after such date of enactment.

- (b) STUDY- The Secretary of Health and Human Services, acting through the Food and Drug Administration, shall conduct a study of the effect on humans of the use of mercury compounds in nasal sprays. Such study shall include data from other studies that have been made of such use.
- (c) STUDY OF MERCURY SALES-
 - (1) STUDY- The Secretary of Health and Human Services, acting through the Food and Drug Administration and subject to appropriations, shall conduct, or shall contract with the Institute of Medicine of the National Academy of Sciences to conduct, a study of the effect on humans of the use of elemental, organic, or inorganic mercury when offered for sale as a drug or dietary supplement. Such study shall, among other things, evaluate—
 - (A) the scope of mercury use as a drug or dietary supplement; and
 - (B) the adverse effects on health of children and other sensitive populations resulting from exposure to, or ingestion or inhalation of, mercury when so used. In conducting such study, the Secretary shall consult with the Administrator of the Environmental Protection Agency, the Chair of the Consumer Product Safety Commission, and the Administrator of the Agency for Toxic Substances and Disease Registry, and, to the extent the Secretary believes necessary or appropriate, with any other Federal or private entity.
 - (2) REGULATIONS- If, in the opinion of the Secretary, the use of elemental, organic, or inorganic mercury offered for sale as a drug or dietary supplement poses a threat to human health, the Secretary shall promulgate regulations restricting the sale of mercury intended for such use. At a minimum, such regulations shall be designed to protect the health of children

and other sensitive populations from adverse effects resulting from exposure to, or ingestion or inhalation of, mercury. Such regulations, to the extent feasible, should not unnecessarily interfere with the availability of mercury for use in religious ceremonies.

SEC. 414. INTERAGENCY COLLABORATION.

Section 903 (21 U.S.C. 393), as amended by section 406, is further amended by inserting after subsection (b) the following:

- ‘(c) INTERAGENCY COLLABORATION- The Secretary shall implement programs and policies that will foster collaboration between the Administration, the National Institutes of Health, and other science-based Federal agencies, to enhance the scientific and technical expertise available to the Secretary in the conduct of the duties of the Secretary with respect to the development, clinical investigation, evaluation, and postmarket monitoring of emerging medical therapies, including complementary therapies, and advances in nutrition and food science.’.

SEC. 415. CONTRACTS FOR EXPERT REVIEW.

Chapter IX (21 U.S.C. 391 et seq.), as amended by section 214, is further amended by adding at the end the following:

‘SEC. 907. CONTRACTS FOR EXPERT REVIEW.

‘(a) IN GENERAL-

- ‘(1) AUTHORITY- The Secretary may enter into a contract with any organization or any individual (who is not an employee of the Department) with relevant expertise, to review and evaluate, for the purpose of making recommendations to the Secretary on, part or all of any application or submission (including a petition, notification, and any other similar form of request) made under this Act for the approval or classification of an article or made under section 351 (a) of the Public Health Service Act (42 U.S.C. 262 (a)) with respect to a biological product. Any such contract shall be subject to the requirements of section 708 relating to the confidentiality of information.
- ‘(2) INCREASED EFFICIENCY AND EXPERTISE THROUGH CONTRACTS- The Secretary may use the authority granted in paragraph (1) whenever the Secretary determines that use of a contract described in paragraph (1) will improve the timeliness of the review of an application or submission described in paragraph (1), unless using such authority would reduce the quality, or unduly increase the cost, of such review. The Secretary may use such authority whenever the Secretary determines that use of such a contract will improve the quality of the review of an application or submission described in paragraph (1), unless using such authority would unduly increase the cost of such review. Such improve-

ment in timeliness or quality may include providing the Secretary increased scientific or technical expertise that is necessary to review or evaluate new therapies and technologies.

‘(b) REVIEW OF EXPERT REVIEW-

‘(1) IN GENERAL- Subject to paragraph (2), the official of the Food and Drug Administration responsible for any matter for which expert review is used pursuant to subsection (a) shall review the recommendations of the organization or individual who conducted the expert review and shall make a final decision regarding the matter in a timely manner.

‘(2) LIMITATION- A final decision by the Secretary on any such application or submission shall be made within the applicable prescribed time period for review of the matter as set forth in this Act or in the Public Health Service Act (42 U.S.C. 201 et seq.).’.

SEC. 416. PRODUCT CLASSIFICATION.

Subchapter E of chapter V, as amended by section 404, is further amended by adding at the end the following:

‘SEC. 563. CLASSIFICATION OF PRODUCTS.

‘(a) REQUEST- A person who submits an application or submission (including a petition, notification, and any other similar form of request) under this Act for a product, may submit a request to the Secretary respecting the classification of the product as a drug, biological product, device, or a combination product subject to section 503 (g) or respecting the component of the Food and Drug Administration that will regulate the product. In submitting the request, the person shall recommend a classification for the product, or a component to regulate the product, as appropriate.

‘(b) STATEMENT- Not later than 60 days after the receipt of the request described in subsection (a), the Secretary shall determine the classification of the product under subsection (a), or the component of the Food and Drug Administration that will regulate the product, and shall provide to the person a written statement that identifies such classification or such component, and the reasons for such determination. The Secretary may not modify such statement except with the written consent of the person, or for public health reasons based on scientific evidence.

‘(c) INACTION OF SECRETARY- If the Secretary does not provide the statement within the 60-day period described in subsection (b), the recommendation made by the person under subsection (a) shall be considered to be a final determination by the Secretary of such classification of the product, or the component of the Food and Drug Administration that will regulate the product, as applicable, and may not be modified by the Secretary except with the written consent of the person, or for public health reasons based on scientific evidence.’.

SEC. 417. REGISTRATION OF FOREIGN ESTABLISHMENTS.

Section 510 (i) (21 U.S.C. 360 (i)) is amended to read as follows:

- ‘(i) (1) Any establishment within any foreign country engaged in the manufacture, preparation, propagation, compounding, or processing of a drug or a device that is imported or offered for import into the United States shall register with the Secretary the name and place of business of the establishment and the name of the United States agent for the establishment.
- ‘(2) The establishment shall also provide the information required by subsection (j).
- ‘(3) The Secretary is authorized to enter into cooperative arrangements with officials of foreign countries to ensure that adequate and effective means are available for purposes of determining, from time to time, whether drugs or devices manufactured, prepared, propagated, compounded, or processed by an establishment described in paragraph (1), if imported or offered for import into the United States, shall be refused admission on any of the grounds set forth in section 801 (a).’.

SEC. 418. CLARIFICATION OF SEIZURE AUTHORITY.

Section 304 (d) (1) (21 U.S.C. 334 (d) (1)) is amended—

- (1) in the fifth sentence, by striking ‘paragraphs (1) and (2) of section 801 (e)’ and inserting ‘subparagraphs (A) and (B) of section 801 (e) (1)’; and
- (2) by inserting after the fifth sentence the following: ‘Any person seeking to export an imported article pursuant to any of the provisions of this subsection shall establish that the article was intended for export at the time the article entered commerce.’.

SEC. 419. INTERSTATE COMMERCE.

Section 709 (21 U.S.C. 379a) is amended by striking ‘a device’ and inserting ‘a device, food, drug, or cosmetic’.

SEC. 420. SAFETY REPORT DISCLAIMERS.

Chapter VII (21 U.S.C. 371 et seq.), as amended by section 412, is further amended by adding at the end the following:

‘SUBCHAPTER G—SAFETY REPORTS.

‘SEC. 756. SAFETY REPORT DISCLAIMERS.

‘With respect to any entity that submits or is required to submit a safety report or other information in connection with the safety of a product (including a product that is a food, drug, device, dietary supplement, or cosmetic) under this Act (and any release by the

Secretary of that report or information), such report or information shall not be construed to reflect necessarily a conclusion by the entity or the Secretary that the report or information constitutes an admission that the product involved malfunctioned, caused or contributed to an adverse experience, or otherwise caused or contributed to a death, serious injury, or serious illness. Such an entity need not admit, and may deny, that the report or information submitted by the entity constitutes an admission that the product involved malfunctioned, caused or contributed to an adverse experience, or caused or contributed to a death, serious injury, or serious illness.’.

Section 301 (21 U.S.C. 331) is amended by striking paragraph (1).

SEC. 422. RULE OF CONSTRUCTION.

Nothing in this Act or the amendments made by this Act shall be construed to affect the question of whether the Secretary of Health and Human Services has any authority to regulate any tobacco product, tobacco ingredient, or tobacco additive. Such authority, if any, shall be exercised under the Federal Food, Drug and Cosmetic Act as in effect on the day before the date of the enactment of this Act.

TITLE V—EFFECTIVE DATE

SEC. 501. EFFECTIVE DATE.

Except as otherwise provided in this Act, this Act, and the amendments made by this Act, other than the provisions of and the amendments made by sections 111, 121, 125, and 307, shall take effect 90 days after the date of enactment of this Act. Speaker of the House of Representatives. Vice President of the United States and President of the Senate.

Appendix B

Components/Repackagers

This section contains some general advice as to contractual elements as between product manufacturers who are vendees and their suppliers, vendors, of packaging, raw materials, product samples, etc.

To the extent that confidential formulas, specifications, etc. must be provided, suitable confidentiality agreements should be mutually signed in advance.

Suppliers should contract to permit inspection of their premises, review controls and analyses, by the vendors at reasonable times and periods. They should also agree to keep vendees informed of governmental inspections and findings as they relate to the subject matter of the agreement.

Suppliers should keep the vendees advised of any changes in premises, equipment, and packaging in accordance with the purchase agreement. Certainly any significant changes made at regulatory demand should immediately be communicated to the vendee.

Indemnification clauses that have been approved by insurance carriers of the parties, risk management, or legal personnel, should also be included in such agreements. If statutory guarantee is to be provided, and it should be wherever appropriate, the contract should include same.

Although it is specifically prohibited in 1.5(h), subsection of section 303(c)(3) of the Act, to represent or suggest that an article is guaranteed under the Act in its labeling, appropriate guaranties should be received with components, including assurance of proper registration with the Food and Drug Administration pursuant to section 510 of the Federal Food, Drug and Cosmetic Act. This can be accomplished by a continuing guaranty as shown in Example A.

Example A

Be advised that the undersigned has accomplished proper registration with the Federal Food and Drug Administration, pursuant to section 510 of the Federal Food, Drug and Cosmetic Act dated _____
FURTHER,

The undersigned hereby guarantees that no food, drug, device, or cosmetic constituting, or being part of, any shipment or other delivery now or hereafter made to you by the undersigned will, at the time of such shipment or delivery, be adulterated or misbranded within the meaning of the Federal Food, Drug and Cosmetic Act, or within the meaning of any applicable state or municipal law in which the definitions of adulteration and misbranding are substantially the same as those contained in the Federal Food, Drug and Cosmetic Act as said Act and such laws are constituted and effective at the time of such shipment or delivery, or will be an article which may not, under the provisions of section 404 or 505 of said Act, be introduced into interstate commerce.

This guaranty shall be a continuing guaranty and shall be binding upon the undersigned with respect to all foods, drugs, devices and cosmetics shipped or delivered to you by the undersigned (including goods in transit), before the receipt by you of written notice of the revocation thereof.

Signed:

Company Name _____

Title _____

Address _____

Dated: _____

[Where appropriate, an additional guaranty may be incorporated:]

“A guaranty is also hereby given that no shipment or delivery now or hereafter made to you by the undersigned will, at the time of such shipment or delivery, be in violation of any of the provisions of the Federal Hazardous Substances Labeling Act.”

If the purchase or shipment involves coal-tar colors and the manufacturer is domestic, the following guaranty should be obtained.

Example B

AS PER SECTION 303(c)(3) OF THE FEDERAL FOOD, DRUG AND COSMETIC ACT.

_____ hereby guarantees that all coal-tar colors listed herein were manufactured by him, and are from batches certified in accordance with the applicable regulations promulgated under the Federal Food, Drug and Cosmetic Act.

Company Name _____

Signature _____

Title _____

Address _____

When a manufacturer of chemicals supplies a raw ingredient to a pharmaceutical manufacturer, it is necessary for the chemical manufacturer to abide by all the requirements of the regulations, if the chemical meets the definition of the drug in section 201(g) of the Act: “articles intended for use as a component” in “articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals.”

COMPONENTS FOR REPACKAGERS: REPACKAGING: EXEMPTIONS FOR DRUGS AND DEVICES—SECTION 503 OF THE FEDERAL FOOD, DRUG AND COSMETIC ACT

The retail or dispensing container of food, drugs, and/or cosmetics, when shipped, or held after shipment, in interstate commerce, must comply with certain labeling and packaging requirements of the Federal Food, Drug and Cosmetic Act. The FDA is directed to promulgate regulations that exempt drugs and devices from the labeling and packaging requirements set out in section 502 and its effectuating regulations.

These are restricted by section 503(a) to drugs and devices that are as a trade practice intended to be processed (undefined), labeled, or repacked.

1. In substantial quantities.
2. At establishments other than those where originally processed or packed.
3. Provided that such drugs and devices are not adulterated or misbranded, according to the criteria of the Act, when they leave this secondary processor, labeler or repacker’s establishment.

To effectuate this legislative directive, the FDA published the 201.150 regulations, which have the effect of law.

Section 201.150(a) notes that the duration of such an exemption extends from the time of introduction into interstate commerce, time actually in interstate commerce (freight or shipment time), and the time it enters and is held in the secondary establishment so they may do the assigned work with it. Such time of exemption from the labeling and packaging requirements of section 501(b) which deals with compendial similarity and labeling, and of 502(b) (address, quantity, and count); 502(d) (habit-forming designation); 502(e) (nonproprietary name and setting out of ingredients); 502(f) directions, usage, warnings; 502(g) compendial requirements.

It is predicated on two alternative factors:

1. The primary shipper is actually the operator of the secondary establishment as well; e.g., the Pfizer plant at Terre Haute sends material to its Groton, Connecticut, plant for further processing, or,
2. If the primary operator is unrelated in ownership to the secondary operator, the shipment must be preceded by a written agreement signed by the parties

and containing their business addresses. This is usually kept, in copy, in the “job jacket.”

This agreement must spell out the specifications for processing, labeling, or repackaging to ensure that as followed the drug or device will as completed be nonviolative of the adulteration or misbranding provisions of the Act. While this can be incorporated in the regular contract between the parties, to do so risks exposure of the total contract to agency inquiry on the basis of their right to examine this writing for two years (both parties) after final shipment or delivery of such drug or device from the establishment.

Bear in mind, that there is no need, legally, nor should it be assumed, that the completed product must be returned to the primary party. Very often it may go immediately to third parties involved with distribution of the product—such as wholesalers, mailing houses, sales agents.

This requirement is one that is all too frequently forgotten with old drugs and devices, and with new drugs. With the latter there are additional requirements per section 505 and the 200 series of regulations (201.150 et seq.).

Section 201.150(b)—subsequent removal from the secondary location of the same operator, of an adulterated or misbranded final product—makes the exemption void ab initio. And it is likewise violative [201.150(c)] if during the 2-year period the FDA is refused inspection of the *copy* of the agreement.

Section 201.150(d) ends any exemption gained under 21.107(a)(2) for similar reasons as 201.150(b) and (c).

Sections 201.150(e), (g), and (h) are somewhat the same as the foregoing for antibiotics, adding exemption from 502(1), which deals with need for batch certification and release.

It should be noted that the exemption is available for interstate shipments of bulk material to be repackaged at an establishment other than where the goods were originally processed provided that such shipment is covered under a written agreement between the one who ships the bulk and the one who repackages it. Records of the agreement (see Example D below) must be kept until two years after the final shipment or delivery of such drug from such an establishment. Copies of these records are to be available for inspection by the FDA. If no agreement is available, or on refusal to show the inspector a copy of such agreement, the exemption shall be declared void ab initio, and all material may be declared misbranded, with appropriate penalty.

Example D

IN ACCORDANCE WITH PARAGRAPH 201.150 OF THE GENERAL REGULATIONS OF THE FOOD, DRUG AND COSMETIC ACT.

The parties, supplier and customer, contemplate that this order, placed and acknowledged, signed by and containing the post office address of the supplier, shall constitute a written agreement within the meaning of paragraph 201.150 of the General Regulations, Federal Food, Drug and Cosmetic Act; that it contains such specifications for the processing, labeling, repackaging, as the case may be, of such drug or device in such establishment as will insure, if specifications are followed, that such drug or device will not be adulterated or misbranded within the meaning of the Act upon completion of such pro-

cessing, labeling, or repacking. It is further understood that this record of agreement will be kept until two years after the final shipment or delivery of such drug from such establishment. Exemption from compliance with the labeling and packaging requirements of sections 501(b) and 502(b), (d), (e), (f) and (g) is claimed thereon.

SEE ATTACHMENTS HERETO, PART OF THIS AGREEMENT:

_____ Company Name _____

_____ Signature _____

_____ Title _____

_____ Address _____

The repackager, to protect himself, may submit for his customer's signature an agreement somewhat similar in scope (Example E).

Example E

_____ (date)

The parties to this agreement, _____ (name)

_____ (address) , and _____ (name)

_____ (address) ;

Being cognizant of the service rendered to _____ (customer)

which involves bulk shipments in interstate commerce of the product(s) hereafter named _____;

And further that the foregoing shipments be sanctioned by an agreement made as provided by regulation under section 405, section 503(a), or section 603 of the Federal Food, Drug and Cosmetic Act;

Agree that they shall use for the immediate container of such products the labels specified and provided, as necessary to bring such products into compliance with said Act before introduction into interstate commerce.

Agree that they shall each keep a copy of this agreement and make such available for official inspection as required by such regulation. The customer guarantees that such products are not articles forbidden entry into interstate commerce under the provisions of section 404 or section 505 of the FFDC Act.

This agreement shall continue until cancelled by either party, on written notice and without prejudice to the other party.

ATTACHMENTS HERETO PART OF THIS AGREEMENT:

Signed for supplier

Signed for customer

(date)

(L. S.) (date)

(L. S.)

(title)

(title)

(address)

(address)

Neither repackager nor his customer need be reluctant to sign agreements D and E above since they are provided for in the regulations, and actually attach, at least commercially, in the form of warranties according to the Uniform Sales Act, Uniform Commercial Code, or specific statutes.

Subpart E—Other Exemptions

§ 201.150 Drugs; processing, labeling, or repacking.

(a) Except as provided by paragraphs (b) and (c) of this section, a shipment or other delivery of a drug which is, in accordance with the practice of the trade, to be processed, labeled, or repacked in substantial quantity at an establishment other than that where originally processed or packed, shall be exempt, during the time of introduction into and movement in interstate commerce and the time of holding in such establishment, from compliance with the labeling and packaging requirements of sections 501(b) and 502(b), (d), (e), (f), and (g) of the act if:

(1) The person who introduced such shipment or delivery into interstate commerce is the operator of the establishment where such drug is to be processed, labeled, or repacked; or

(2) In case such person is not such operator, such shipment or delivery is made to such establishment under a written agreement, signed by and containing the post-office addresses of such person and such operator, and containing such specifications for the processing, labeling, or repacking, as the case may be, of such drug in such establishment as will insure, if such specifications are followed, that such drug will not be adulterated or misbranded within the meaning of the act upon completion of such processing, labeling, or repacking. Such person and such operator shall each keep a copy of such agreement until 2 years after the final shipment or delivery of such drug from such establishment, and shall make such copies available for inspection at any reasonable hour to any officer or employee of the Department who request them.

(b) An exemption of a shipment or other delivery of a drug under paragraph (a)(1) of this section shall, at the beginning of the act of removing such shipment or delivery, or any part thereof, from such establishment, become void ab initio if the drug comprising such shipment, delivery, or part is adulterated or misbranded within the meaning of the act when so removed.

(c) An exemption of a shipment or other delivery of a drug under paragraph (a)(2) of this section shall become void ab initio with respect to the person who introduced such shipment or delivery into interstate commerce upon refusal by such person to make available for inspection a copy of the agreement, as required by such paragraph (a)(2) of this section.

(d) An exemption of a shipment or other delivery of a drug under paragraph (a)(2) of this section shall expire:

(1) At the beginning of the act of removing such shipment or delivery, or any part thereof, from such establishment if the drug comprising such shipment, delivery, or part is adulterated or misbranded within the meaning of the act when so removed; or (2) Upon refusal by the operator of the establishment where such drug is to be processed, labeled, or repacked, to make available for inspection a copy of the agreement, as required by such clause.

(e) Except as provided in paragraphs (g) and (h) of this section, a shipment or other delivery of a drug which is subject to section 507 of the act and which is, in accordance with the practice of the trade, to be processed or repacked in a substantial quantity at an establishment other than that where originally processed or packed shall be exempt from compliance with the labeling requirements of section 502(f) of the act during the time such drug is also exempt from the requirements of section 502(1) of the act or, in the case of a new animal drug, is exempt from certification under section 512(n) of the act under the provisions of § 433.15 or § 433.16 of this chapter.

(f) Except as provided by paragraphs (g) and (h) of this section, a shipment or other delivery of a drug which is subject to section 507 of the act and which is, in accordance with the practice of the trade, to be labeled in substantial quantity at an establishment other than that where originally processed or packed shall be exempt from compliance with the labeling requirements of section 502(b), (e) and (f) of the act during the time such drug is also exempt from the requirements of section 502(1) of the act or, in the case of a new animal drug, is exempt from certification under section 512(n) of the act under § 433.12 of this chapter, if the words, statements, and other information required by section 502(b) and (e) of the act appear on each shipping container of such drug.

(g) In case the person who introduced such shipment or other delivery into interstate commerce is the operator of the establishment where such drug is to be processed, labeled, or repacked, an exemption of such shipment or delivery under paragraph (e) or (f) of this section shall become void at the beginning of the act of removing such shipment or delivery or any part thereof from such establishment.

NEW DRUG APPLICATIONS; DRUG MASTER FILES

Attached herewith, for your information, is a notice taken from the *Federal Register* dated Monday, July 3, 1995 (60 FR 34486) proposing to revise its regulations governing drug master files (DMFs), which are referred to in the review and approval of new drugs and antibiotic drugs for human use.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 314

[Docket No. 94N-0449]

New Drug Applications; Drug Master Files

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to revise its regulations governing drug master files (DMF's), which are referred to in the review and approval of new drugs and antibiotic drugs for human use. A DMF is a voluntary submission to FDA that may be used to provide confidential, detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of one or more human drugs. The information contained in a DMF may be referred to in support of an investigational new drug application (IND), a new drug application (NDA), an abbreviated new drug application (ANDA), or amendments or supplements to any of these. FDA has defined five distinct categories of submissions that it will accept and maintain, and it has designated these as Type I through Type V DMF's.

In December 1992, the Center for Drug Evaluation and Research's (CDER's) Chemistry, Manufacturing, Controls Coordinating Committee (CMCCC) established a DMF Task Force to perform a review and to explore ways of improving all aspects of the system. One of the Task Force recommendations, which was adopted by the CMCCC, was to eliminate Type I DMF's. Type I DMF's contain information about manufacturing sites, facilities, operating procedures, and personnel. The Task Force concluded that Type I DMF's should be eliminated because they contain outdated information, duplicate information contained in marketing applications, and are not used by CDER's review divisions or FDA's field inspectors. Under the proposed rule, FDA would no longer permit information submitted in a Type I DMF to be incorporated by reference in IND's, NDA's, ANDA's, abbreviated antibiotic applications (AADA's), and supplemental applications. This proposed rule is intended to eliminate submissions of information that are not necessary either to conduct inspections of manufacturing facilities or to review the chemistry, manufacturing, and controls sections of IND's, NDA's, and abbreviated applications. This proposed rule would not apply to master file systems that are operated by the Center for Biologics Evaluation and Research, the Center for Veterinary Medicine, and Center for Device and Radiological Health.

DATES: Written comments by October 2, 1995. FDA proposes that any final rule based on this proposal become effective 60 days after its date of publication in the Federal Register.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Howard P. Muller, Center for Drug Evaluation and Research (HFD-362), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301-594-1046.

SUPPLEMENTARY INFORMATION:

I. Introduction

DMF's allow regulated industry to submit to FDA information that may be used to support an IND, NDA, ANDA, AADA, another DMF, an export application, or amendments or supplements to any of these. FDA does not require industry to submit DMF's; a DMF is submitted solely at the discretion of the holder. DMF's allow industry to provide confidential, detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of drugs for human use. This information is then incorporated by reference in a drug application or supplement without public disclosure.

FDA regulations in § 314.420(a) (21 CFR 314.420(a)) define five types of DMF's according to the kind of information to be submitted. Type I submissions include manufacturing site, facilities, operating procedures, and personnel information. Type II submissions include information regarding drug substances, drug substance intermediates, and materials used to prepare them, or drug products. Type III submissions include information about packaging material. Type IV submissions include information concerning excipients, colorants, flavors, and essences, or material used in their preparation. Type V submissions, detailed in the "Guideline for Drug Master Files" (1989), include FDA-accepted reference information

Under § 314.420, FDA recommended that foreign drug manufacturing facilities file with FDA information concerning their manufacturing sites, facilities, operating procedures, and personnel in a Type I DMF. FDA requested this information to plan its on-site inspections of and travel to foreign drug manufacturing facilities. FDA believed that inspections would be conducted more efficiently if FDA inspectors knew in advance the location, plant layout, equipment type, and personnel at the foreign manufacturing site. FDA did not request that domestic firms submit Type I DMF's because FDA inspectors regularly visit firms in their district and are familiar with both their personnel and manufacturing sites. Nonetheless, some domestic pharmaceutical firms have submitted Type I DMF's. Currently, CDER has approximately 1,700 Type I DMF's.

Recently, FDA evaluated the usefulness of Type I DMF's. The agency determined that its inspectors were not using Type I DMF's to plan foreign inspections because the Type I DMF was not easily accessible or information contained in the Type I DMF was outdated. Instead, FDA now requests foreign firms to submit a preinspection document package that includes both current facility and product-specific information. FDA inspectors use the preinspection package to plan their inspection. Although submission of the package is voluntary, foreign firms comply with the agency's request because the information helps inspectors to conduct inspections quickly and efficiently. The agency concluded that Type I DMF's could be eliminated without adversely affecting inspections of foreign manufacturing facilities.

FDA has also determined that its review divisions do not rely on Type I DMF's. Although Type I DMF's are often incorporated by reference into IND's, NDA's, and abbreviated applications, the information that the agency requested to be submitted under

Type I DMF's is not required for chemistry, manufacturing, and controls review. Under 21 CFR 314.50(d)(1)(i) and (d)(1)(ii), a drug product applicant is required to furnish the name and location of facilities used in the manufacture of the drug substance or product. Unlike a Type I DMF submission, this information, when submitted as part of an application, is current and product-specific. Therefore, review divisions rely on the applications themselves for this information.

Accordingly, the agency proposes to amend § 314.420 to eliminate Type I DMF's. The agency would no longer accept new Type I DMF's, or correspondence updating existing Type I DMF's. The information in Type I DMF's currently on file could no longer be incorporated by reference into new applications, amendments, or supplements, and the Type I DMF's would be transferred to the Federal Records Center, Suitland, MD. These proposed changes would supersede all information regarding Type I DMF's detailed in the "Guideline for Drug Master Files."

The agency acknowledges that some firms may have submitted information under a Type I DMF that should have been filed under Types II through V DMF's. Therefore, FDA is proposing to make available a list of all CDER Type I DMF's for public review in the Dockets Management Branch under the docket number found in brackets in the heading of this document. If a DMF holder believes that its Type I DMF should be categorized as another type of DMF, the DMF holder should submit a request to the Drug Master File Staff, Food and Drug Administration, rm. 2-14, 12420 Parklawn Dr., Rockville, MD 20857, within 30 days of publication of any final rule based on this proposal. This request should: (1) Be submitted by the responsible official or designated U.S. agent; (2) briefly identify the subject of the DMF; and (3) propose the DMF Type (i.e., Type II, III, IV, or V) to which information in the Type I DMF should be transferred. If the information should be incorporated into an existing Type II through Type V DMF, the file number of that DMF should be provided. FDA would consider transferring an entire Type I DMF to another type only if the Type I DMF contains substantive information other than information concerning manufacturing site, facilities, operating procedures, and personnel.

The agency also recognizes that some Type I DMF's currently on file contain information concerning sterilization process validation and other information relevant to the review, evaluation, and assurance of the sterility of sterile products. For sterile items that are not the subject of an IND, NDA, ANDA, or AADA, and that are sold to a second party (e.g., rubber closures that are sterilized by the manufacturer and sold to a second party), CDER would consider transferring product-specific and general information concerning sterilization process validation to the DMF file or DMF type (i.e., II through IV) under which manufacturing information for the specific item is filed. Contract manufacturers of sterile finished drug products, contract sterilization firms (e.g., ethylene oxide, gamma radiation, and electron beam radiation), and manufacturers of sterile finished drug products that are the subject of a drug product application could request a transfer from Type I to Type V DMF of nonproduct-specific information and procedures that are submitted to support a claim of sterility. Where applicable, the content and format of such transferred information should follow FDA's guideline entitled "Guideline for Submitting Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products." The mechanism for requesting a transfer would be the same as the mechanism for recategorizing Type I DMF's, as described in the preceding paragraph.

II. Environmental Impact

The agency has determined under 21 CFR 25.24(a)(8) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

III. Analysis of Impacts

FDA has examined the impacts of the proposed rule under Executive Order 12866 and the Regulatory Flexibility Act (Pub. L. 96-354). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety and other advantages; distributive impacts; and equity). The agency believes that this proposed rule is consistent with the regulatory philosophy and principles identified in the Executive Order. In addition, the proposed rule is not a significant regulatory action as defined by the Executive Order and so is not subject to review under the Executive Order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because the proposed regulation, if finalized, would lighten paperwork and recordkeeping burdens, the agency certifies that the proposed rule will not have a significant economic impact on a substantial number of small entities. Therefore, under the Regulatory Flexibility Act, no further analysis is required.

IV. Effective Date

FDA proposes that any final rule based on this proposal become effective 60 days after its date of publication in the Federal Register.

V. Request for Comments

Interested persons may, on or before October 2, 1995, submit to the Dockets Management Branch (address above) written comments regarding this proposal. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

List of Subjects in 21 CFR Part 314

Administrative practice and procedure, Confidential business information, Drugs, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR part 314 be amended as follows:

PART 314—APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG OR AN ANTIBIOTIC DRUG

1. The authority citation for 21 CFR part 314 continues to read as follows:

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 701, 704, 721 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 371, 374, 379e).

2. Section 314.420 is amended by removing and reserving paragraph (a)(1), and by revising the second sentence of paragraph (a)(5) to read as follows:

§ 314.420 Drug master files.

(a) * * *

(1) [Reserved]

* * * * *

(5) * * * (A person wishing to submit information and supporting data in a drug master file (DMF) that is not covered by Types II through IV DMF's must first submit a letter of intent to the Drug Master File Staff, Food and Drug Administration, 12420 Parklawn Dr., rm. 2-14, Rockville, MD 20857. * * *)

* * * * *

Dated: June 26, 1995.

William B. Schultz,

Deputy Commissioner for Policy.

[FR Doc. 95-16206 Filed 6-30-95; 8:45 am]

BILLING CODE 4160-01-F

FDA GUIDANCE DOCUMENT CONCERNING USE OF PILOT MANUFACTURING FACILITIES FOR THE DEVELOPMENT AND MANUFACTURE OF BIOLOGICAL PRODUCTS; AVAILABILITY

Attached herewith, for your information, is a notice taken from the *Federal Register* dated Tuesday, July 11, 1995 (60 FR 35750) announcing the availability of a guidance document concerning the use of pilot facilities for the development and manufacture of biological products.

Food and Drug Administration

[Docket No. 95D-0164]

FDA Guidance Document Concerning Use of Pilot Manufacturing Facilities for the Development and Manufacture of Biological Products; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing the availability of a guidance document concerning the use of pilot facilities for the development and manufacture of biological products. The guidance document, entitled "Center for Biologics Evaluation and Research; Use of Pilot Manufacturing Facilities for the Development and Manufacture of Biological Products; Guidance," provides guidance by the Center for Biologics Evaluation and Research (CBER) to manufacturers of biological products to

clarify the licensing requirements for the use of small scale and pilot facilities for the development and manufacture of biological products. These facilities are sometimes collectively referred to by industry as pilot facilities. This guidance document is intended to provide increased flexibility for industry without diminishing public health protection.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857. Comments should be identified with the docket number found in brackets in the heading of the document. Two copies of all comments are to be submitted, except that individuals may submit one copy. The comments received are available for public examination in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

FOR FURTHER INFORMATION CONTACT: Jean M. Olson, Center for Biologics Evaluation and Research (HFM-630), Food and Drug Administration, 1401 Rockville Pike, suite 400 South, Rockville, MD 20852-1448, 301-594-3074.

SUPPLEMENTARY INFORMATION: CBER recognizes that development of important new biological products is expensive and time consuming, and that companies must be able to forecast and evaluate their expenditures for this process. Constructing a new facility to manufacture a product that has not been fully tested in clinical trials could result in a company being unable to recover a major capital expenditure if the product is not ultimately brought to market. CBER also recognizes that for some companies the best financial option may be the use of a pilot facility where a product may be manufactured at a smaller scale than would be ultimately desired for an approved product.

While CBER does not object to the use of pilot production facilities for the manufacture of clinical material, many companies are concerned that these facilities would not be eligible for establishment licensure. This guidance document is intended to clearly articulate that pilot facilities are eligible for licensure. The guiding principle is that an application for establishment licensure can be made for any facility (regardless of the scale of manufacture) which is fully qualified, validated, operates in accordance with current good manufacturing practices (CGMP's), and otherwise complies with applicable law and regulations. In order to further streamline the approval process, the agency is currently considering changing its procedures to eliminate the requirement for a separate establishment license for certain well defined classes of biologic products. Because of recent scientific advances, both in methods of manufacture and in methods of analysis, some products developed through biotechnology can be characterized in ways not historically considered possible. Thus, the agency is considering allowing "biotech" products that are well characterized to be regulated under a single application. The agency plans to hold a scientific conference in the fall of 1995, to develop a definition of well characterized products that may be amenable to regulation under new procedures.

This guidance document describes the conditions and procedures for submitting establishment license applications (ELA's) for pilot facilities and for subsequent transfer of product manufacturing to a different facility. The guidance document provides information concerning: (1) Use of a product manufactured in a pilot facility in clinical trials conducted to demonstrate safety and effectiveness and optional transition to a different facility; (2) submissions for approval to use a pilot facility for manufacture of a product;

(3) submissions for approval to use a different manufacturing facility while a product license application (PLA) for a product manufactured in a pilot facility and an ELA for a pilot facility are pending; (4) submissions for approval to use a different manufacturing facility when a product and pilot facility are currently licensed; and (5) submission of a PLA based on data obtained from a product made in a pilot facility when licensure of the product manufactured in the pilot facility and of the pilot facility is not sought.

The guidance also addresses review timeframes and submission times, product consistency, data comparing products made in different facilities, and product availability at the time of product licensure.

In addition, FDA intends to revise the policy statement entitled “Manufacturing Arrangements for Licensed Biologics” published in the Federal Register of November 25, 1992 (57 FR 55544) to accommodate these procedures.

This guidance document is not binding on either FDA or manufacturers of biological products and does not create or confer any rights, privileges, or benefits for or on any person.

Interested persons may submit to the Dockets Management Branch (address above) written comments on the guidance document. Received comments will be considered to determine if further revision to the guidance document is necessary.

The title and text of the guidance document follows:

Center for Biologics Evaluation and Research; Use of Pilot Manufacturing Facilities for the Development and Manufacture of Biological Products; Guidance

I. Introduction

Biological products, which generally include vaccines, blood and blood products, allergenic extracts, and biological therapeutics, are regulated under section 351 of the Public Health Service Act (the PHS Act) (42 U.S.C. 262), as well as the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321). The PHS Act requires that biological products be propagated or manufactured and prepared at an establishment holding an unsuspended and unrevoked license. Lack of clarity about licensing requirements has led some applicants to make major investments in large scale manufacturing facilities before initiating the clinical trial(s) necessary to demonstrate the safety and effectiveness of their products. Such investments can result in significant financial loss if the product is not ultimately brought to market. In this document, the Center for Biologics Evaluation and Research (CBER) is providing guidance to manufacturers and developers of biological products to clarify licensing procedures for the use of pilot facilities for the manufacture of biological products. CBER considers a pilot production to be a procedure and facility fully representative of and simulating that to be applied on a full commercial scale. For example, the methods of cell expansion, harvest, and product purification should be identical except for scale of production. These facilities are sometimes collectively referred to by industry as “pilot facilities” and will be referred to as “pilot” in this document. These facilities are to be distinguished from facilities used in research and development that may not operate under appropriate current good manufacturing practices (CGMP’s).

II. Background

CBER recognizes that development of important new biological products may be expensive and time consuming and that companies must be able to forecast and evaluate

their expenditures for this process. Constructing a large scale facility to manufacture a product that has not been fully tested in clinical trials could result in a major capital loss if delays occur or the product is not ultimately brought to market. CBER also recognizes that for some companies, the best financial option may be the use of a pilot facility where a product may be manufactured at a smaller scale than might be eventually desired for an approved product. While CBER has not objected to the use of pilot facilities for the manufacture of clinical material (provided such manufacture is in compliance with requirements applicable to investigational drugs), many companies are concerned that these facilities and the product manufactured in them would not be eligible for licensure. An application for establishment licensure can be made for any facility (regardless of the scale of manufacture) that has been fully qualified and validated, that operates under CGMP's, and that otherwise complies with applicable laws and regulations. This guidance document describes the conditions and procedures for submitting such application(s) and for subsequent, optional transfer of product manufacturing to a different manufacturing facility.

III. Guidance

The following provides information on the submission of product license applications (PLA's) and establishment license applications (ELA's) and investigational new drug applications (IND's) for products manufactured in a pilot facility.

1. Use of a product manufactured in a pilot facility in clinical trials conducted to demonstrate safety and effectiveness and optional transition to a different facility.

IND's for all products should include information that describes where the material for the clinical trial(s) used to demonstrate safety and effectiveness is or was manufactured. Data submitted in support of licensure of a biological product can be obtained using a product manufactured in a pilot facility. In the event that a product manufactured in new facilities and/or scaled-up processes or facilities is intended to be used at a later date for either completion of the clinical trial(s) demonstrating safety or effectiveness or for licensable product, the time tables, new locations, and processes should be identified in the IND. A protocol for comparing products should also be submitted. Data which compares a product made in a new facility or with new processes to a product used in earlier clinical studies should be submitted to the IND before including the new product in the clinical trial(s). If the product made in the new facility or by the new process will not be used in the clinical trials used to demonstrate safety or effectiveness, the data comparing the two products should be submitted in the IND, PLA, or PLA supplement. A description of any manufacturing changes that were made as a result of using a new facility or new processes and stability data should also be submitted to the IND or PLA as appropriate.

2. Submissions for approval to use a pilot facility for manufacture of a product.

Information and data submitted in the PLA should be obtained using a product manufactured in the pilot facility. The ELA should include a completed Form FDA 3210; Application for Establishment License for Manufacture of Biological Products (FDA Form 3210), which describes the pilot facility. If the facility is already licensed, an ELA supplement that contains information specific to the new product should be submitted. The facility and equipment, regardless of scale, should have undergone appropriate qualification and validation and should be in compliance with applicable regulations, including, but

not limited to, 21 CFR parts 210, 211, 600 and 820. A prelicense inspection will be conducted prior to the approval of the PLA and ELA or ELA supplement. The PLA and ELA may be submitted at different times, provided a statement is included in any PLA or ELA submission confirming that the facility is ready for inspection and indicating the approximate date for the companion application submission. CBER intends to review PLA's and ELA's submitted at different times under the normal timeframe targets of the managed review process (from the date of receipt at CBER, 12 months for standard applications, 6 months for priority applications, and 6 months for supplements). Because CBER issues the ELA and PLA concurrently, timing of submission of the companion applications should be carefully considered. CBER intends to consider failure to submit a companion application within 6 months of receipt of a standard application or 3 months of receipt of a priority application to be grounds for issuing a not approvable letter to the applicant.

3. Submissions for approval to use a different manufacturing facility while a PLA for a product manufactured in a pilot facility and an ELA for a pilot facility are pending.

In this case, a PLA for a product made in a pilot facility and ELA for the pilot facility are under review as outlined in section III. 2 of this guidance. FDA's inspection of the pilot facility may or may not have occurred. The applicant is now requesting licensure of a different facility in addition to, or in lieu of, licensure of the pilot facility. The following information should be submitted to the pending PLA: a description of manufacturing changes which have occurred, data comparing products made in the new and old facilities, and documentation of process validation and stability data for a product manufactured in the new facility. CBER intends to consider the submission to be a separate PLA filing that will be assigned a new reference number and a 6-month review timeframe. A new ELA that contains a completed ELA Form 3210 describing the new facility should also be submitted. If the new facility is already licensed, the applicant should submit a supplement to the approved ELA with the information specific to the new product. A statement confirming that the new facility is ready for inspection should be included in the new PLA filing and the ELA or ELA supplement at the time of submission. Concurrent review of the pilot facility will continue unless the applicant is no longer requesting approval to market lots manufactured in the pilot facility. If the applicant does not wish to pursue licensure of lots made in a pilot facility, a request may be made in writing that the pending ELA for the pilot facility be withdrawn; however, FDA may still conduct an inspection. In this case, lots manufactured in the pilot facility could be used in other clinical trials but could not be marketed. CBER intends to review the ELA for the new facility within new application timeframes under the managed review process. As such, CBER intends to issue a new reference number and review priority applications within 6 months, standard applications within 12 months, and supplements within 6 months. CBER intends to review the new PLA filing within 6 months. An inspection of both facilities will be performed if the applicant requests licensure of both. Applicants should specify which establishment is a higher priority for licensure and CBER may choose to concentrate its resources on reviewing the application for that facility first. Either combination of product and establishment may be licensed when all information has been reviewed and found to be acceptable. The pilot facility and product may be eligible for licensure before the new facility and product are ready for approval. In regard to the timing of submissions, it should be noted that CBER's timeframe for review of a new ELA may be longer (12

months for standard application and 6 months for priority application under the managed review process) than that for review of the new PLA filing. CBER intends to consider failure to submit a companion application within 6 months of receipt of a standard application or 3 months of receipt of a priority application to be grounds for issuing a not approvable letter to the applicant.

4. Submissions for approval to use a different manufacturing facility when a product and pilot facility are currently licensed.

A supplement to the approved PLA for a product made in a pilot facility and an ELA or ELA supplement for the new facility should be submitted when the applicant wishes to obtain licensure for a different facility and product manufactured in it. The PLA supplement should contain information on a product manufactured in the new facility, including a description of manufacturing changes that have occurred. (See “Changes to be Reported for Product and Establishment License Applications; Guidance” (60 FR 17535, April 6, 1995)). Data comparing products made in each facility, and process validation and stability data for a product manufactured in the new facility should also be provided. If a new ELA is submitted, it should contain a completed ELA Form 3210 that describes the new facility. If the proposed facility is already a licensed facility, an ELA supplement should be submitted that contains information specific to the new product. A statement confirming that the facility is ready for inspection should be included with each submission. CBER intends to review PLA’s, ELA’s, and supplements according to the timeframe targets of the managed review process (6 months for manufacturing and facility changes) and intends to approve ELA’s and PLA’s or supplements concurrently, when all information has been reviewed and found acceptable. CBER intends to consider failure to submit a companion application within 6 months of receipt of a standard application or 3 months of receipt of a priority application to be grounds for issuing a not approvable letter to the applicant.

5. Submission of a PLA based on data obtained from a product made in a pilot facility when licensure of the product manufactured in the pilot facility and pilot facility is not sought.

CBER will allow submission of a PLA based on data obtained from clinical trials using a product made in a pilot facility when the pilot facility is not intended to be licensed. In order to verify data comparing a product made in a pilot facility and used in the clinical trials to a product made in the facility to be licensed, the pilot facility should be available for inspection up to the time the applicant obtains licensure of the product in the new facility. A product used in clinical trials to support licensure can be made in a facility for which the applicant does not intend to seek licensure, but only a licensed product made in a licensed facility may be marketed. The PLA should contain information and data on a product manufactured in the pilot facility and a statement that the pilot facility is ready for inspection at the time of submission. An inspection of the pilot facility may be performed in some cases. Stability data from a product made in the pilot facility, if representative of a product manufactured in the facility intended to be licensed, can be used in support of a proposed dating period. A separate, original ELA for the facility intended for licensure may be submitted concurrently with the PLA or after review of the PLA has begun. The ELA for the facility intended for licensure should be submitted when a product

in support of approval has been manufactured, a product is available for review, and the facility is ready for inspection. If submission of the ELA occurs after PLA review has begun, an accompanying PLA supplement containing data comparing products made in both facilities should include stability data, process validation, and a description of any manufacturing changes (see Guidance (60 FR 17535)). CBER intends to review each ELA and PLA under the current timeframe targets of the managed review process (from the date of receipt at CBER, 12 months for standard and 6 months for priority applications; 6 months for manufacturing supplements). While an ELA and PLA need not be submitted concurrently, applicants are reminded that CBER intends to approve ELA's and PLA's concurrently. CBER intends to consider failure to submit a companion application within 6 months of receipt of a standard application or 3 months of receipt of a priority application to be grounds for issuing a not approvable letter to the applicant.

6. Demonstration of product consistency and data comparing products made in different facilities.

When manufacture of a product is transferred from a pilot facility to a different facility, a demonstration of product consistency, data comparing the two products, and process validation should be submitted in the PLA supplement or amendment to the IND. Retention samples from the pilot facility should be stored under controlled conditions in sufficient quantity to conduct the side-by-side testing of products. Applicants are encouraged to discuss with CBER what data are necessary to compare products, as such data may range from analytical testing to full clinical trial(s).

7. Review timeframes and submission times

There may be cases where applicants wish to submit an ELA for a pilot facility prior to submitting a companion PLA. A statement that the facility is ready for inspection at the time of submission should be included. FDA ordinarily intends to inspect at the time the facility is manufacturing the product for which licensure is sought. It is possible that, in some cases, inspection of the establishment could take place before the submission of the PLA. It is also possible for the ELA to be submitted after the PLA as discussed above.

CBER intends to review PLA's and ELA's submitted at different times under the normal timeframe targets of the managed review process (from the date of receipt at CBER, 12 months for standard and 6 months for priority applications; 6 months for supplements). CBER intends to issue the appropriate action letter (approved, approvable, or not approvable) to complete its action on any application.

Applicants should be aware that submitting the ELA and PLA at separate times will not necessarily reduce the approval time when compared to concurrent submission. Early submission of applications may, however, allow earlier feedback from CBER on deficiencies in an application that can be addressed by the applicant sooner than would otherwise be possible. In all cases described above, CBER intends to approve PLA's, ELA's, or supplements concurrently.

In cases of shared manufacturing arrangements (see 57 FR 55544 at 55545), the PLA's for the intermediate product(s) and end product should be submitted concurrently in order for a complete review of the product to occur, since determining the approvability

of the end product will depend upon information in the intermediate product PLA's. The ELA's may be submitted at different times from the PLA's.

Applicants should consider carefully the consequences of the timing of any submission on the use of CBER resources. It is expected that applicants will use the flexible submission times in cases of need. Applicants should recognize that the filing of submissions which are premature or incomplete will result in unnecessary resource commitments by CBER and the applicant. It is therefore recommended that applicants do not submit an ELA before favorable preliminary data or information from clinical trials of the product is available. For products intended for use in serious and life-threatening diseases, applicants should consider submitting the ELA and PLA concurrently to prevent a situation from occurring where otherwise approvable product cannot be approved because the facility is not yet ready to be licensed.

If a scenario exists that is not covered in this guidance document, the applicant should seek guidance by contacting the appropriate applications division in the Offices of Therapeutics Research and Review, Blood Research and Review, or Vaccines Research and Review, or the Division of Establishment Licensing.

8. Availability of product at the time of licensure

If an applicant requests licensure for a pilot facility, this choice may affect the amount of product available at the time of approval. For important new products for use in treating serious and life-threatening illnesses, the ramifications of limited availability of the product at the time of approval should be assessed by the applicant.

Dated: June 26, 1995.
William B. Schultz,
Deputy Commissioner for Policy.
[FR Doc. 95-17022 Filed 7-7-95; 10:53 am]
BILLING CODE 4160-of-F

Food and Drug Administration

[Docket No. 94D-0029]

International Conference on Harmonization; Draft Guideline on the Extent of Population Exposure Required to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is publishing a draft guideline entitled "The Extent of Population Exposure Required to Assess Clinical Safety for Drugs Intended for Long-term Treatment of Non-life-threatening Conditions." This draft guide-

line was prepared by the Expert Group on Efficacy of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The draft guideline is intended to present an accepted set of principles for the safety evaluation of drugs intended for the long-term treatment (chronic or repeated intermittent use for longer than 6 months) of non-life-threatening diseases.

DATES: Submit written comments by May 16, 1994.

ADDRESSES: Submit written comments on the draft guideline to the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT:

Regarding the draft guideline: Leah Ripper, Center for Drug Evaluation and Research (HFD-500), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-2544.

Regarding ICH: Janet Showalter, Office of Health Affairs (HFY-50), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-1382.

SUPPLEMENTARY INFORMATION: In recent years, many important initiatives have been undertaken by regulatory authorities and industry associations to promote harmonization of regulatory requirements. FDA has participated in many meetings designed to enhance harmonization and is committed to seeking scientifically based harmonized technical procedures for pharmaceutical development. One of the goals of harmonization is to identify and then reduce differences in technical requirements for drug development.

ICH was organized to provide an opportunity for tripartite harmonization initiatives to be developed with input from both regulatory and industry representatives. FDA also seeks input from consumer representatives and other interested parties. Through notices such as this, FDA invites public comment on ICH initiatives that have reached the draft guideline stage. ICH is concerned with harmonization of technical requirements for the registration of pharmaceutical products among three regions: the European Union, Japan, and the United States. The six ICH sponsors are the European Commission, the European Federation of Pharmaceutical Industry Associations, the Japanese Ministry of Health and Welfare, the Japanese Pharmaceutical Manufacturers Association, FDA, and the U.S. Pharmaceutical Manufacturers Association. The ICH Secretariat, which coordinates the preparation of documentation, is provided by the International Federation of Pharmaceutical Manufacturers Associations (IFPMA).

The ICH Steering Committee includes representatives from each of the organizing bodies and IFPMA, as well as observers from the World Health Organization, the Canadian Health Protection Branch, and the European Free Trade Area.

At a meeting held from October 27 through 29, 1993, the ICH Steering Committee agreed that a draft tripartite guideline entitled "Draft Guideline on the Extent of Population Exposure Required to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions" should be made available for public comment. The draft guideline will be made available for comment by the European Commission and Japanese Ministry of Health and Welfare, as well as by FDA, in accordance with their

respective consultation procedures. After analyzing the comments and revising the guideline if appropriate, FDA will determine whether it will adopt and issue the guideline.

The draft guideline presents an accepted set of principles for the safety evaluation of drugs intended for the long-term treatment of non-life-threatening diseases. The draft guideline distinguishes between clinical data on adverse drug events (ADE's) derived from studies of shorter duration and of exposure and data from studies of longer duration, which frequently include nonconcurrently controlled studies. The principles discussed in the draft guideline are summarized as follows: (1) Regulatory standards are valuable for the extent and duration of treatment needed to provide the safety data base for drugs intended for long-term treatment of non-life-threatening conditions; however, there are a number of circumstances where harmonized regulatory standards for the clinical safety evaluation may not be applicable; (2) further investigation is needed about the occurrence of ADE's in relation to duration of treatment for different drug classes; (3) because most ADE's first occur within the first 3 to 6 months of drug treatment, many patients should be treated and observed for 6 months at dosage levels intended for clinical use; and (4) because some serious ADE's may occur only after drug treatment for more than 6 months, some patients should be treated with the drug for 12 months.

Guidelines are generally issued under §§ 10.85(d) and 10.90(b) (21 CFR 10.85(d) and 10.90(b)), which provide for the use of guidelines to establish procedures or standards of general applicability that are not legal requirements but that are acceptable to FDA. The agency is now in the process of considering whether to revise §§ 10.85(d) and 10.90(b). Therefore, if the agency issues this guideline in final form, the guideline would not be issued under the authority of §§ 10.85(d) and 10.90(b), and would not create or confer any rights, privileges, or benefits for or on any person, nor would it operate to bind FDA in any way.

Interested persons may, on or before May 16, 1994, submit written comments on the draft guideline to the Dockets Management Branch (address above). Two copies are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

The text of the draft guideline follows:
The Extent of Population Exposure Required to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions.

The objective of this guideline is to present an accepted set of principles for the safety evaluation of drugs intended for the longterm treatment (chronic or repeated intermittent use for longer than 6 months) of non-life-threatening diseases. The safety evaluation during clinical drug development is expected to characterize and quantify the safety profile of a drug over a reasonable duration of time consistent with the intended long-term use of the drug. Thus, duration of drug exposure and its relationship to both time and magnitude of occurrence of adverse events are important considerations in determining the size of the data base necessary to achieve such goals.

For the purpose of this guideline, it is useful to distinguish between clinical data on adverse drug events (ADEs) derived from studies of shorter duration of exposure and

data from studies of longer duration, which frequently are non-concurrently controlled studies. It is expected that short-term event rates (cumulative 3 month incidence of about 1%) will be well characterized. Events where the rate of occurrence changes over a longer period of time may need to be characterized depending on their severity and importance to the risk-benefit assessment of the drug. The safety evaluation during clinical drug development is not expected to characterize rare adverse events, for example, those occurring in less than 1 in 1,000 patients.

The design of the clinical studies can significantly influence the ability to make causality judgments about the relationships between the drug and adverse events. A placebo-controlled trial allows the adverse event rate in the drug-treated group to be compared directly with the background event rate in the patient population being studied. Although a study with a positive or active control will allow a comparison of adverse event rates to be made between the test drug and the control drug, no direct assessment of the background event rate in the population studied can be made. A study that has no concurrent control group makes it more difficult to assess the causality relationship between adverse events observed and the test drug.

There was general agreement on the following:

1. A harmonized regulatory standard is of value for the extent and duration of treatment needed to provide the safety data base for drugs intended for long-term treatment of non-life-threatening conditions. Although this standard covers many indications and drug classes, there are exceptions.

2. Regulatory standards for the safety evaluation of drugs should be based on previous experience with the occurrence and detection of adverse drug events (ADEs), statistical considerations of the probability of detecting specified frequencies of ADEs, and practical considerations.

3. Information about the occurrence of ADEs in relation to duration of treatment for different drug classes is incomplete, and further investigations to obtain this information would be useful.

4. Available information suggests that most ADEs first occur, and are most frequent, within the first few months of drug treatment. The number of patients treated for 6 months at dosage levels intended for clinical use should be adequate to characterize the pattern of ADEs over time.

To achieve this objective the cohort of exposed subjects should be large enough to observe whether more frequently occurring events increase or decrease over time as well as to observe delayed events of reasonable frequency (e.g., in the general range of 0.5%–5%). Usually from 300–600 patients should be adequate.

5. There is concern that, although they are likely to be uncommon, some ADEs may increase in frequency or severity with time or that some serious ADEs may occur only after drug treatment for more than 6 months. Therefore, some patients should be treated with the drug for 12 months. In the absence of more information about the relationship of ADEs to treatment duration, selection of a specific number of patients to be followed for 1 year is to a large extent a judgment based on the probability of detecting a given ADE frequency level and practical considerations.

100 patients exposed for a minimum of 1 year is considered to be acceptable to include as part of the safety data base. The data should come from prospective studies

appropriately designed to provide at least one year exposure at dosage levels intended for clinical use. When no serious ADE is observed in a one year exposure period this number of patients can provide reasonable assurance that the true cumulative 1-year incidence is no greater than 3%.

6. It is anticipated that the total number of individuals treated with the investigational drug, including short-term exposure, will be about 1500. Japan currently accepts 500–1500 patients; the potential for a smaller number of patients is due to the post-marketing surveillance requirement, the actual number for a specific drug being determined by the information available on the drug and drug class.

7. There are a number of circumstances where the harmonized general standards for the clinical safety evaluation may not be applicable. Reasons for, and examples of, these exceptions are listed below. It is expected that additional examples may arise. It should also be recognized that the clinical data base needed for efficacy testing may be occasionally larger or may give rise to a need for longer patient observation than that acceptable under this guideline.

Exceptions:

a. Instances where there is concern that the drug will cause late developing ADEs, or cause ADEs that increase in severity or frequency over time, would result in a need for a larger and/or longer-term safety data base. The concern could arise from:

- (1) data from animal studies;
- (2) clinical information from other agents with related chemical structures or from a related pharmacologic class; and
- (3) pharmacokinetic or pharmacodynamic properties known to be associated with such ADEs.

b. Situations in which there is a need to quantitate the occurrence rate of an expected specific low frequency ADE will result in a need for a greater long-term data base. Examples would include situations where a specific serious ADE has been identified in similar drugs or where a serious event that could represent an alert event is observed in early clinical trials.

c. Larger safety data bases may be needed to make risk/benefit decisions in situations where the benefit from the drug is either: (1) small (e.g., symptomatic improvement in less serious medical conditions) or (2) will be experienced by only a fraction of the treated patients (e.g., certain preventive therapies administered to healthy populations) or; (3) is of uncertain magnitude (e.g., efficacy determination on a surrogate endpoint).

d. In situations where there is concern that a drug may add to an already significant background rate of morbidity or mortality, clinical trials may need to be designed with a sufficient number of patients to provide adequate statistical power to detect prespecified increases over the baseline morbidity or mortality.

e. In some cases, a smaller number of patients may be acceptable, for example, where the intended treatment population is small.

8. Filing for approval will usually be possible based on the data from patients treated through 6 months. Data on patients treated through 12 months are to be submitted as soon as available and prior to approval in the United States and Japan but may be submitted after approval in the E.C. In the U.S. the initial submission for those drugs designated as priority drugs is expected to include the 12 months patient data.

Dated: February 23, 1994.

Michael R. Taylor,

Deputy Commissioner for Policy

[FR Doc. 94-4567 Filed 2-24-94; 1:35 pm]

BILLING CODE 4160-01-F

[Docket No. 94D-0028]

International Conference on Harmonization; Draft Guideline on Repeated Dose Tissue Distribution Studies; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is publishing a draft guideline entitled "Pharmacokinetics: Guidance for Repeated Dose Tissue Distribution Studies." The draft guideline was prepared by the Safety Expert Working Group of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The draft guideline is intended to provide guidance on the circumstances when repeated dose tissue distribution studies should be considered and on the conduct of those studies.

DATES: Written comments by May 16, 1994.

ADDRESSES: Submit written comments on the draft guideline to the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT:

Regarding the draft guideline: Alan S. Taylor, Center for Drug Evaluation and Research (HFD-502), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-2544.

Regarding ICH: Janet Showalter, Office of Health Affairs (HFY-50), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-1382.

SUPPLEMENTARY INFORMATION: In recent years, many important initiatives have been undertaken by regulatory authorities and industry associations to promote harmonization of regulatory requirements. FDA has participated in many meetings designed to enhance harmonization and is committed to seeking scientifically based harmonized technical procedures for pharmaceutical development. One of the goals of harmonization is to identify and then reduce differences in technical requirements for drug development.

ICH was organized to provide an opportunity for tripartite harmonization initiatives to be developed with technical input from both regulatory and industry representatives. FDA also seeks input from consumer representatives and other interested parties. Through notices such as this, FDA invites public comment on ICH initiatives that have reached the draft guideline stage. ICH is concerned with harmonization of technical requirements for the registration of pharmaceutical products among three regions: the European Union, Japan, and the United States. The six ICH sponsors are the European Commission, the

European Federation of Pharmaceutical Industry Associations, the Japanese Ministry of Health and Welfare, the Japanese Pharmaceutical Manufacturers Association, FDA, and the U.S. Pharmaceutical Manufacturers Association. The ICH Secretariat, which coordinates the preparation of documentation, is provided by the International Federation of Pharmaceutical Manufacturers Associations (IFPMA).

The ICH Steering Committee includes representatives from each of the ICH sponsors and IFPMA, as well as observers from the World Health Organization, the Canadian Health Protection Branch, and the European Free Trade Area.

At a meeting held from October 27 through 29, 1993, the ICH Steering Committee agreed that the draft tripartite guideline entitled "Toxicokinetics: Guidance for Repeated Dose Tissue Distribution Studies" should be made available for public comment. The draft guideline will be made available for comment by the European Commission and Japanese Ministry of Health and Welfare, as well as by FDA, in accordance with their respective consultation procedures. After analyzing the comments and revising the guideline, if appropriate, FDA will determine whether it will adopt and issue the guideline.

The draft guideline recommends that repeated dose tissue distribution studies should not be required uniformly for all compounds and should only be conducted when appropriate data cannot be derived from other sources. Repeated dose studies may be appropriate for compounds which have: (1) An apparently long half life; (2) incomplete elimination; or (3) unanticipated organ toxicity. The draft guideline provides general guidance on the use of radio-labelled compounds, dose and species selection, and duration of studies.

Guidelines are generally issued under §§ 10.85(d) and 10.90(b) (21 CFR 10.85(d) and 10.90(b)), which provide for the use of guidelines to establish procedures or standards of general applicability that are not legal requirements but that are acceptable to FDA. The agency is now in the process of considering whether to revise §§ 10.85(d) and 10.90(b). Therefore, if the agency issues this guideline in final form, it would not be issued under the authority of §§ 10.85(d) and 10.90(b), and would not create or confer any rights, privileges, or benefits for or on any person, nor would it operate to bind FDA in any way.

Interested persons may, on or before May 16, 1994, to the Dockets Management Branch (address above) submit written comments on the draft guideline. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. The draft guideline and received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

The text of the draft guideline follows:

Pharmacokinetics: Guidance for Repeated Dose Tissue Distribution Studies

I. Introduction

A comprehensive knowledge of the absorption, distribution, metabolism, and elimination of a compound is important for the interpretation of pharmacology and toxicology studies. Tissue distribution studies are essential in providing information on distribution and accumulation of the compound and/or metabolites especially in relation to potential sites of action. This information may be useful for designing toxicology and pharmacology studies and for interpreting the results of these experiments.

In the European Community, the United States, and Japan, there has been a general agreement on the need to conduct single dose tissue distribution studies as part of the

preclinical package. These studies often provide sufficient information about tissue distribution.

There has been no consistent requirement for repeated dose tissue distribution studies. However, there may be circumstances when assessments after repeated dosing may yield important information.

This paper provides guidance on circumstances when repeat dose tissue distribution studies should be considered and on the conduct of such studies.

II. Circumstances Under Which Repeated Dose Tissue Distribution Studies Should Be Considered

1. When information is available to predict that accumulation of a compound will occur in organs and tissues after repeated administration, then the extent and the time course of accumulation and elimination should be examined by repeated dose tissue distribution studies. For example, when single dose tissue distribution studies suggest that the apparent half life of the test compound (and/or metabolites) in organs or tissues significantly exceeds the apparent half life of the elimination phase in plasma and is more than twice the dosing interval in the toxicity studies, repeated dose studies may be appropriate.

2. When repeated dose pharmacokinetic or toxicokinetic data suggest an accumulation of the compound and/or metabolites, which was not predicted by single dose kinetic studies, repeated dose tissue distribution studies should be considered.

3. When patho-morphological changes are observed that would not be predicted from short term toxicity studies and single dose tissue distribution studies, repeated dose tissue distribution studies may aid in the interpretation of these findings. Those organs or tissues which were the site of the lesions should be the focus of such studies.

III. Design and Conduct of Repeated Dose Tissue Distribution Studies

1. The objectives of these studies may be achieved using radio-labelled compounds or alternative methods of sufficient sensitivity and specificity.

2. Dose level(s) and species should be chosen to address the problem that led to the consideration of the repeated dose tissue distribution study.

3. Information from previous pharmacokinetic and toxicokinetic studies should be used in selecting the duration of dosing in repeated dose tissue distribution studies. One week of dosing is normally considered to be a minimum period. A longer duration should be selected when the blood/plasma concentration of the drug and/or its metabolites does not reach steady state. It is normally considered unnecessary to dose for longer than 3 weeks.

4. Consideration should be given to measuring unchanged compound and/or metabolites in organs and tissues in which extensive accumulation occurs or if it is believed that such data may clarify mechanisms of organ toxicity.

IV. Conclusions

Tissue distribution studies are an essential component in the preclinical kinetics programme. For most compounds, it is expected that single dose tissue distribution studies with sufficient sensitivity and specificity will provide an adequate assessment of tissue distribution and the potential for accumulation. Thus, repeated dose tissue distribution studies should not be required uniformly for all compounds. Repeated dose studies may

be appropriate under certain circumstances based on the data from single dose tissue distribution studies, toxicity and toxicokinetic studies. The studies may be most appropriate for compounds which have an apparently long half life, incomplete elimination or unanticipated organ toxicity. The design and timing of repeated dose tissue distribution studies should be determined on a case-by-case basis.

Dated: February 23, 1994.

Michael R. Taylor,

Deputy Commissioner for Policy.

[FR Doc. 94-4568 Filed 2-24-94; 1:35 pm]

BILLING CODE 4160-01-F

[Docket No. 94D-0016]

International Conference on Harmonization; Draft Guideline on Validation of Analytical Procedures for Pharmaceuticals; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is publishing a draft guideline on the validation of analytical procedures for pharmaceuticals. This draft guideline was prepared by the Expert Working Group on Quality of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). This draft guideline is intended to present characteristics that should be considered during the validation of the analytical procedures included as part of registration applications for pharmaceuticals.

DATES: Written comments by May 16, 1994.

ADDRESSES: Submit written comments on the draft guideline to the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT:

Regarding the draft guideline: Charles S. Kumkumian, Center for Drug Evaluation and Research (HFD-102), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4330.

Regarding ICH: Janet Showalter, Office of Health Affairs (HFY-50), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-1382.

SUPPLEMENTARY INFORMATION: In recent years, many important initiatives have been undertaken by regulatory authorities and industry associations to promote harmonization of regulatory requirements. FDA has participated in many meetings designed to enhance harmonization and is committed to seeking scientifically based harmonized techni-

cal procedures for pharmaceutical development. One of the goals of harmonization is to identify and then reduce differences in technical requirements for drug development.

ICH was organized to provide an opportunity for tripartite harmonization initiatives to be developed with input from both regulatory and industry representatives. FDA also seeks input from consumer representatives and other interested parties. Through notices such as this, FDA invites public comment on ICH initiatives that have reached the draft guideline stage. ICH is concerned with harmonization of technical requirements for the registration of pharmaceutical products among three regions: The European Union, Japan, and the United States. The six ICH sponsors are the European Commission, the European Federation of Pharmaceutical Industry Associations, the Japanese Ministry of Health and Welfare, the Japanese Pharmaceutical Manufacturers Association, FDA, and the U.S. Pharmaceutical Manufacturers Association. The ICH Secretariat, which coordinates the preparation of documentation, is provided by the International Federation of Pharmaceutical Manufacturers Associations (IFPMA).

The ICH Steering Committee includes representatives from each of the ICH sponsors and IFPMA, as well as observers from the World Health Organization, the Canadian Health Protection Branch, and the European Free Trade Area.

At a meeting held from October 27 through 29, 1993, the ICH Steering Committee agreed that a draft tripartite guideline entitled “Draft Guideline on Validation of Analytical Procedures” should be made available for public comment. The draft guideline will be made available for comment by the European Commission and Japanese Ministry of Health and Welfare, as well as by FDA, in accordance with their respective consultation procedures. After analyzing the comments and revising the guideline if appropriate, FDA will determine whether it will adopt and issue the guideline.

The draft guideline presents a discussion of the characteristics that should be considered during the validation of the analytical procedures included as part of registration applications submitted in Europe, Japan, and the United States. The draft guideline discusses common types of analytical procedures and defines basic terms, such as “analytical procedure,” “specificity,” and “precision.” These terms and definitions are meant to bridge the differences that often exist between various compendia and regulators of the European Union, Japan, and the United States.

Guidelines are generally issued under §§ 10.85(d) and 10.90(b) (21 CFR 10.85(d) and 10.90(b)), which provide for the use of guidelines to establish procedures or standards of general applicability that are not legal requirements but that are acceptable to FDA. The agency is now in the process of considering whether to revise § 10.85(d) and § 10.90(b). Therefore, if the agency issues this guideline in final form, the guideline would not be issued under the authority of § 10.85(d) and § 10.90(b) and would not create or confer any rights, privileges, or benefits for or on any person, nor would it operate to bind FDA in any way.

Interested persons may, on or before May 16, 1994, submit to the Dockets Management Branch (address above) written comments on the draft guideline. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

The text of the draft guideline follows:

Text on Validation of Analytical Procedures

1. Introduction

This document presents a discussion of the characteristics that should be considered during the validation of the analytical procedures included as part of registration applications submitted within Europe, Japan, and the United States. This document does not necessarily seek to cover the testing that may be required for registration in, or export to, other areas of the world. Furthermore, this text presentation serves as a collection of terms, and their definitions, and is not intended to provide direction on how to accomplish validation. These terms and definitions are meant to bridge the differences that often exist between various compendia and regulators of Europe, Japan, and the United States.

The objective of validation of an analytical procedure is to demonstrate that it is suitable for its intended purpose. A tabular summation of the characteristics applicable to identification, control of impurities and assay procedures is included. Other analytical procedures may be considered in future additions to this document.

2. Types of Analytical Procedures to be Validated

The discussion of the validation of analytical procedures is directed to the four most common types of analytical procedures:

- Identification tests.
- Quantitative measurements for impurities' content.
- Limit tests for the control of impurities.
- Quantitative measure of the active moiety in samples of drug substance or drug product or other selected component(s) in the drug product.

Although there are many other analytical procedures, such as dissolution testing for drug products or particle size determination for drug substance, these have not been addressed in the initial text on validation of analytical procedures. Validation of these additional analytical procedures is equally important to those listed herein and may be addressed in subsequent documents.

A brief description of the types of tests considered in this document is provided below.

- Identification tests are intended to ensure the identity of an analyte in a sample. This is normally achieved by comparison of a property of the sample (e.g. spectrum, chromatographic behavior, chemical reactivity, etc) to that of a reference standard.
- Impurity tests can be either a quantitative test or a limit test for the impurity in a sample. Either test is intended to accurately reflect the purity characteristics of the sample. Different validation characteristics are needed for a quantitative test than for a limit test.
- Assay procedures are intended to measure the analyte present in a given sample. In the context of this document, the assay represents a quantitative measurement of the major component(s) in the drug substance. For the drug product, similar validation characteristics also apply when assaying for the active or other selected component(s). The same validation characteristics may also apply to assays associated with other analytical procedures (e.g. dissolution).

The objective of the analytical procedure should be clearly understood since this will govern the validation characteristics which need to be evaluated. Typical validation characteristics which should be considered are listed below:

Accuracy;

Precision;

 Repeatability,

 Intermediate precision,

 Reproducibility;

Specificity;

Detection limit;

Quantitation limit;

Linearity;

Range.

Each of these validation characteristics is defined in the attached Glossary. Table 1 (p. 142) lists those validation characteristics regarded as the most important for the validation of different types of analytical procedures. This list should be considered typical for the analytical procedures cited but occasional exceptions should be dealt with on a case by case basis. It should be noted that robustness is not listed in the table but should be considered at an appropriate stage in the development of the analytical procedure.

Annex

Glossary

1. Analytical Procedure

The analytical procedure is a detailed description of the steps necessary to perform each analytical test. This may include but is not limited to: the sample, the reference standard and the reagents preparations, use of the apparatus, generation of the calibration curve, and use of the formulae for the calculation, etc.

2. Specificity

Specificity is the ability to assess unequivocally the analyte in the presence of components which may be expected to be present. Typically these might include impurities, degradants, matrix, etc.

Lack of specificity of an individual analytical procedure may be compensated by other supporting analytical procedure(s).

This definition has the following implications:

Identification: to ensure the identity of an analyte.

Purity Tests: to ensure that all the analytical procedures performed allow an accurate statement of the content of impurities of an analyte, i.e. related substances test, heavy metals, residual solvents content, etc.

Assay (content or potency); to provide an exact result which allows an accurate statement on the content or potency of the analyte in a sample.

3. Accuracy

The accuracy of an analytical procedure expresses the closeness of agreement between the value which is accepted either as a conventional true value or an accepted reference value and the value found.

4. Precision

The precision of an analytical procedure expresses the closeness of agreement (degree of scatter) between a series of measurements obtained from multiple sampling of the same homogeneous sample under the prescribed conditions. Precision may be performed at three levels: repeatability, intermediate precision and reproducibility.

Precision should be measured using authentic samples. However, if it is not possible to obtain a homogeneous sample it may be measured using artificially prepared samples or a sample solution.

The precision of an analytical procedure is usually expressed as the variance, standard deviation or coefficient of variation of a series of measurements.

4.1 Repeatability

Repeatability expresses the precision under the same operating conditions over a short interval of time. Repeatability is also termed intra-assay precision.

4.2 Intermediate precision

Intermediate precision expresses within laboratories variations: different days, different analysts, different equipment, etc.

4.3 Reproducibility

Reproducibility expresses the precision between laboratories (collaborative studies).

5. Detection Limit

The detection limit of an individual analytical procedure is the lowest amount of analyte in a sample which can be detected but not necessarily quantitated as an exact value.

6. Quantitation Limit

The quantitation limit of an individual analytical procedure is the lowest amount of analyte in a sample which can be quantitatively determined with suitable precision and accuracy. The quantitation limit is a parameter of quantitative assays for low levels of compounds in sample matrices, and is used particularly for the determination of impurities and/or degradation products.

7. Linearity

The linearity of an analytical procedure is its ability (within a given range) to obtain test results which are directly proportional to the concentration (amount) of analyte in the sample.

For those analytical procedures which are not linear, another mathematical relationship (proportionality) should be demonstrated.

8. Range

The range of an analytical procedure is the interval between the upper and lower concentration (amounts) of analyte in the sample (including these concentrations) for which it has been demonstrated that the analytical procedure has a suitable level of precision, accuracy, and linearity.

9. Robustness

The robustness of an analytical procedure is a measure of its capacity to remain unaffected by small, but deliberate variations in method parameters and provides an indication of its reliability during normal usage.

Dated: February 23, 1994.

Michael R. Taylor,

Deputy Commissioner for Policy.

[FR Doc. 94-4565 Field 2-24-94; 1:35 pm]

BILLING CODE 4160-01-F

[Docket No. 94D-0017]

International Conference on Harmonization; Draft Guideline on Dose Selection for Carcinogenicity Studies of Pharmaceuticals; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is publishing a draft guideline on dose selection for carcinogenicity studies of pharmaceuticals. This draft guideline examines criteria for establishing uniformity among international regulatory agencies for high dose selection for carcinogenicity studies of human pharmaceuticals. This draft guideline was prepared by the Expert Working Group on Safety of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), and it is intended to help ensure that dose selection for carcinogenicity studies of pharmaceuticals to support drug registration is carried out according to sound scientific principles.

DATES: Written comments by May 16, 1994.

ADDRESSES: Submit written comments on the draft guideline to the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT:

Regarding the draft guideline: Alan Taylor, Center for Drug Evaluation and Research (HFD-502), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-2544.

Regarding ICH: Janet Showalter, Office of Health Affairs (HFY-50), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-1382.

SUPPLEMENTARY INFORMATION: In recent years, many important initiatives have been undertaken by regulatory authorities and industry associations to promote international harmonization of regulatory requirements. FDA has participated in many meetings designed to enhance harmonization and is committed to seeking scientifically based harmonized technical procedures for pharmaceutical development. One of the goals of harmonization is to identify and then reduce differences in technical requirements for drug development.

ICH was organized to provide an opportunity for tripartite harmonization initiatives to be developed with input from both regulatory and industry representatives. FDA also

seeks input from consumer representatives and other interested parties. Through notices such as this, FDA invites public comment on ICH initiatives that have reached the draft guideline stage. ICH is concerned with harmonization of technical requirements for the registration of pharmaceutical products among three regions: The European Union, Japan, and the United States. The six ICH sponsors are the European Commission, the European Federation of Pharmaceutical Industry Associations, the Japanese Ministry of Health and Welfare, the Japanese Pharmaceutical Manufacturers Association, FDA, and the U.S. Pharmaceutical Manufacturers Association. The ICH Secretariat, which coordinates the preparation of documentation, is provided by the International Federation of Pharmaceutical Manufacturers Associations (IFPMA).

The ICH Steering Committee includes representatives from each of the ICH sponsors and IFPMA, as well as observers from the World Health Organization, the Canadian Health Protection Branch, and the European Free Trade Area.

At a meeting held from October 27 through 29, 1993, the ICH Steering Committee agreed that the draft tripartite guideline entitled ‘‘Dose Selection for Carcinogenicity Studies of Pharmaceuticals’’ should be made available for public comment. The draft guideline will be made available for comment by the European Commission and Japanese Ministry of Health and Welfare, as well as by FDA, in accordance with their respective consultation procedures. After analyzing the comments and revising the guideline, if appropriate, FDA will determine whether it will adopt and issue the guideline. The draft guideline discusses criteria for high dose selection for carcinogenicity studies of pharmaceuticals. Five generally acceptable criteria are dose limiting pharmacodynamic effects, maximum tolerated dose, a minimum of a 25-fold area under the concentration-time curve (AUC) ratio (rodent: human), saturation of absorption, and maximum feasible dose. The draft guideline also considers other pharmacodynamic-, pharmacokinetic-, or toxicity-based endpoints in study design based on scientific rationale and individual merits.

Guidelines are generally issued under §§ 10.85(d) and 10.90(b) (21 CFR 10.85(d) and 10.90(b)), which provide for the use of guidelines to establish procedures or standards of general applicability that are not legal requirements but that are acceptable to FDA. The agency is now in the process of considering whether to revise §§ 10.85(d) and 10.90(b). Therefore, if the agency issues the guideline in final form, the guideline would not be issued under the authority of §§ 10.85(d) and 10.90(b), and would not create or confer any rights, privileges, or benefits for or on any person, nor would it operate to bind FDA in any way.

Interested persons may, on or before May 16, 1994, submit written comments on the draft guideline to the Dockets Management Branch (address above). Two copies of any comments are to be submitted, except that individuals may submit single copies. Comments are to be identified with the docket number found in brackets in the heading of this document. The draft guideline and received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

The text of the draft guideline follows:

Dose Selection for Carcinogenicity Studies of Pharmaceuticals

Introduction

Traditionally, carcinogenicity studies for chemical agents have relied upon the maximally tolerated dose (MTD) as the standard method for high dose selection (Note 1).

The MTD is generally chosen based on data derived from toxicity studies of 3 months' duration.

In the past, the criteria for high dose selection for carcinogenicity studies of human pharmaceuticals have not been uniform among international regulatory agencies. In Europe and Japan, dose selection based on toxicity endpoints or attaining high multiples of the maximum recommended human daily dose (greater than 100 times on a milligram per kilogram (mg/kg) basis) have been accepted. However, in the United States, dose selection based on the MTD has traditionally been the only acceptable practice. All regions have used a maximum feasible dose as an acceptable endpoint (Note 2).

For pharmaceuticals with low rodent toxicity, use of the MTD may result in the administration of very large doses in carcinogenicity studies, often representing high multiples of the clinical dose. The usefulness of an approach developed for genotoxic substances or radiation exposure where a threshold carcinogenic dose is not necessarily definable may not be appropriate for nongenotoxic agents. For nongenotoxic substances where thresholds may exist and carcinogenicity may result from alterations in normal physiology, linear extrapolations from high dose effects have been questioned. This has led to the concern that exposures in rodents greatly in excess of the intended human exposures may not be relevant to human risk, because they so greatly alter the physiology of the test species, the findings may not reflect what would occur following human exposure.

Ideally, the doses selected for rodent bioassays for nongenotoxic pharmaceuticals should provide exposures to the agent that: (1) Allow an adequate margin of safety over the human therapeutic exposure, (2) are tolerated without significant chronic physiological dysfunction and are compatible with good survival, (3) are guided by a comprehensive set of animal and human data that focuses broadly on the properties of the agent and the suitability of the animal, and (4) permit data interpretation in the context of clinical use.

In order to achieve international harmonization of requirements for high dose selection for carcinogenicity studies of pharmaceuticals, and to establish a rational basis for high dose selection, the ICH Expert Working Group on Safety initiated a process to arrive at mutually acceptable and scientifically based criteria for high dose selection. Several features of pharmaceutical agents distinguish them from other environmental chemicals and can justify a guideline which may differ in some respects from other guidelines. This should enhance the relevance of the carcinogenicity study for pharmaceuticals. Thus, much knowledge may be available on the pharmacology, pharmacokinetics, and metabolic disposition in humans. In addition, there will usually be information on the patient population, the expected use pattern, the range of exposure, and the toxicity and/or side effects that cannot be tolerated in humans. Diversity of the chemical and pharmacological nature of the substances developed as pharmaceuticals, plus the diversity of nongenotoxic mechanisms of carcinogenesis calls for a flexible approach to dose selection. This document proposes that any one of several approaches may be appropriate and acceptable for dose selection, and should provide for a more rational approach to dose selection for carcinogenicity studies for pharmaceuticals. These include:

1. Pharmacodynamic endpoints.
2. Toxicity-based endpoints.
3. Pharmacokinetic endpoints.
4. Saturation of absorption.
5. Maximum feasible dose.

Consideration of all relevant animal data and integration with available human data is paramount in determining the most appropriate endpoint for selecting the high dose for the carcinogenicity study. Relevant pharmacokinetic, pharmacodynamic and toxicity data should always be considered in the selection of doses for the carcinogenicity study regardless of the primary endpoint used for high dose selection.

In the process of defining such a flexible approach, it is recognized that the fundamental mechanisms of carcinogenesis are only poorly understood at the present time. Further, it is also recognized that the use of the rodent to predict human carcinogenic risk has inherent limitations although this approach is the best available option at this time. Thus, while the use of plasma levels of drug-derived substances represents an important attempt at improving the design of the rodent bioassay, progress in this field will necessitate continuing examination of the best method to detect human risk. This document is therefore intended to serve as guidance in this difficult and complex area recognizing the importance of updating the specific provisions outlined below as new data become available.

General Considerations for the Conduct of Dose-Ranging Studies

The considerations involved when undertaking dose-ranging studies to select the high dose for carcinogenicity studies are the same regardless of the final endpoint utilized.

1. In practice, carcinogenicity studies are carried out in a limited number of rat and mouse strains for which there are reasonable information on spontaneous tumor incidence. Ideally, rodent species/strains with metabolic profiles as similar as possible to humans should be studied (Note 3).
2. Dose-ranging studies should be conducted for both males and females for all strains and species to be tested in the carcinogenicity bioassay.
3. Dose selection is generally determined from 90-day studies using the route and method of administration that will be used in the bioassay.
4. Selection of an appropriate dosing schedule and regimen should be based on clinical use and exposure patterns, pharmacokinetics, and practical considerations.
5. Ideally, both the toxicity profile and any dose-limiting toxicity should be characterized. Consideration should also be given to general toxicity, the occurrence of preneoplastic lesions and/or tissue-specific proliferative effects, and disturbances in endocrine homeostasis.
6. Changes in metabolite profile or alterations in metabolizing enzyme activities (induction or inhibition) over time, should be understood to allow for appropriate interpretation of studies.

Pharmacodynamic Endpoints in High Dose Selection

The utility and safety of many therapeutics depend on their pharmacodynamic receptor selectivity. Pharmacodynamic endpoints for high dose selection will be highly compound-specific and are considered for individual study designs based on scientific merits (Note 10). The high dose selected should not produce disturbances of physiology or homeostasis but should produce a pharmacodynamic response in dosed animals which would preclude further dose escalation and compromise the validity of the study.

Toxicity Endpoints in High Dose Selection

ICH 1 agreed to evaluate endpoints other than the MTD for the selection of the high dose in carcinogenicity studies. These were to be based on the pharmacological properties and toxicological profile of the test compound. There is no scientific consensus for the use of toxicity endpoints other than the MTD. Therefore, the ICH Expert Working Group on Safety has currently agreed to continue use of the MTD as an acceptable toxicity-based endpoint for high dose selection for carcinogenicity studies (Note 1).

Pharmacokinetic Endpoints in High Dose Selection

A systemic exposure representing a large multiple of the human AUC (at the maximum recommended daily dose) may be an appropriate endpoint for dose selection for carcinogenicity studies for nongenotoxic therapeutic agents which have similar metabolic profiles in humans and rodents and low organ toxicity in rodents (high doses are well tolerated in rodents). The level of animal systemic exposure should be sufficiently great, compared to human exposure, to provide reassurance of an adequate test of carcinogenicity.

It is recognized that the doses administered to different species may not correspond to tissue concentrations because of different metabolic and excretory patterns. Comparability of systemic exposure is better assessed by blood concentrations of parent drug and metabolites than by administered dose. The unbound drug in plasma is thought to be the most relevant indirect measure of tissue concentrations of unbound drug. The AUC is considered the most comprehensive pharmacokinetic endpoint since it takes into account the plasma concentration of the compound and residence time in vivo.

There is as yet, no validated scientific basis for use of comparative drug plasma concentrations in animals and humans for the assessment of carcinogenic risk to humans. However, for the present, and based on an analysis of a database of carcinogenicity studies performed at the MTD, the selection of a high dose for carcinogenicity studies which represents at a minimum a 25-fold ratio of rodent to human plasma AUC of parent compound and/or metabolites is considered pragmatic (Note 4).

Criteria for comparisons of AUC in animals and man for use in high dose selection

The following criteria are especially applicable for use of a pharmacokinetically-defined exposure for high dose selection.

1. Rodent pharmacokinetic data are derived from the strains used for the carcinogenicity studies using the route of compound administration and dose ranges planned for the carcinogenicity study (Notes 5, 6, and 7).
2. Pharmacokinetic data are derived from studies of sufficient duration to take into account potential time-dependent changes in pharmacokinetic parameters which may occur during the dose ranging studies.
3. Documentation is provided on the similarity of exposure to parent compound and metabolites between rodents and humans.
4. In assessing exposure, scientific judgment is used to determine whether the AUC comparison is based on data for the parent, parent and metabolite(s) or metabolite(s). The justification for this decision is provided.

5. Interspecies differences in protein binding are taken into consideration when estimating relative exposure (Note 8).
6. Human pharmacokinetic data are derived from studies encompassing the maximum recommended human daily dose (Note 9).

Saturation of Absorption in High Dose Selection

High dose selection based on saturation of absorption measured by systemic availability of drug-related substances is acceptable. The mid and low doses selected for the carcinogenicity study should take into account saturation of metabolic and elimination pathways.

Additional Endpoints in High Dose Selection

It is recognized that there may be merit in the use of alternative pharmacokinetic (e.g. C_{max}) and toxicity endpoints, not specifically defined in this guidance on high dose selection for rodent carcinogenicity studies. Use of these additional endpoints in individual study designs should be justified. Such designs are evaluated based on their individual merits (Note 10).

Selection of Middle and Low Doses in Carcinogenicity Studies

Regardless of the method used for the selection of the high dose, the selection of the mid and low doses for the carcinogenicity study should provide information to aid in assessing the relevance of study findings to humans. The doses should be selected following integration of rodent and human pharmacokinetic, pharmacodynamic, and toxicity data. The rationale for the selection of these doses should be provided. While not all-encompassing, the following points should be considered in selection of the middle and low doses for rodent carcinogenicity studies:

1. Linearity of pharmacokinetics and saturation of metabolic pathways,
2. Human exposure and therapeutic dose,
3. Pharmacodynamic response in rodents,
4. Alterations in normal rodent physiology,
5. Mechanistic information and potential for threshold effects,
6. The unpredictability of the progression of toxicity observed in short term studies.

Summary

This guidance outlines five equally acceptable criteria for selection of the high dose for carcinogenicity studies of pharmaceuticals: dose limiting pharmacodynamic effects, maximum tolerated dose, a minimum of a 25-fold AUC ratio (rodent: human), saturation of absorption, maximum feasible dose. The use of other pharmacodynamic-, pharmacokinetic- or toxicity-based endpoints in study design is considered based on scientific rationale and individual merits. In all cases, appropriate dose ranging studies need to be conducted. All relevant information should be considered for dose and species/strain selection for the carcinogenicity study. This information should include knowledge of human use, exposure patterns and metabolism. The availability of multiple acceptable criteria for dose selection will provide greater flexibility in optimizing the design of carcinogenicity studies for pharmaceutical agents.

Note 1

The following are considered equivalent definitions of the toxicity based endpoint describing the maximum tolerated dose:

The U.S. Interagency Staff Group on Carcinogens has defined the MTD as follows:

“The highest dose currently recommended is that which, when given for the duration of the chronic study, is just high enough to elicit signs of minimal toxicity without significantly altering the animal’s normal lifespan due to effects other than carcinogenicity. This dose, sometimes called the maximum tolerated dose (MTD), is determined in a sub-chronic study (usually 90 days duration) primarily on the basis of mortality, toxicity and pathology criteria. The MTD should not produce morphologic evidence of toxicity of a severity that would interfere with the interpretation of the study. Nor should it comprise so large a fraction of the animal’s diet that the nutritional composition of the diet is altered, leading to nutritional imbalance.”

“The MTD was initially based on a weight gain decrement observed in the sub-chronic study; i.e., the highest dose that caused no more than a 10% weight gain decrement. More recent studies and the evaluation of many more bioassays indicate refinement of MTD selection on the basis of a broader range of biological information. Alternations in body and organ weight and clinically significant changes in hematologic, urinary, and clinical chemistry measurements can be useful in conjunction with the usually more definitive toxic, pathologic or histopathologic endpoints.” (See *Environmental Health Perspectives*, vol. 67:201–181, 1986.)

The Committee on Proprietary Medicinal Products of the European Communities prescribes the following: “The top dose should produce a minimum toxic effect, for example a 10% weight loss or failure of growth, or minimal target organ toxicity. Target organ toxicity will be demonstrated by failure of physiological functions and ultimately by pathological changes.” (See “Rules Governing Medicinal Products in the European Communities,” vol. III, 1987.)

The Ministry of Health and Welfare in Japan prescribes the following:

“The dose in the preliminary carcinogenicity study that inhibits body weight gain by less than 10% in comparison with the control and causes neither death due to toxic effects nor remarkable changes in the general signs and laboratory examination findings of the animals is the highest dose to be used in the full-scale carcinogenicity study.” (See “Toxicity Test Guideline for Pharmaceuticals,” chapter 5, p. 127, 1985.)

Note 2

Currently, the maximum feasible dose by dietary administration is considered 5 percent of the diet.

Note 3

This does not imply that all possible rodent strains will be surveyed for metabolic profile. But rather, that standard strains used in carcinogenicity studies will be examined.

Note 4

In order to select a multiple of the human AUC that would serve as an acceptable endpoint for dose selection for carcinogenicity studies, a retrospective analysis was performed on data from FDA files of carcinogenicity studies of products conducted at the MTD for which there was sufficient human and rodent pharmacokinetic data for comparison of AUC values. (See Contrera et al., “Report to the ICH Safety Working Group Task Force on Dose Selection for Carcinogenicity Studies.”)

In 35 drug carcinogenicity studies carried out at the MTD for which there was adequate pharmacokinetic data in rats and humans, approximately 1/3 had a relative systemic exposure ratio equal to or less than 1, and another 1/3 had a ratio greater than 1 and less than 10 at the MTD.

An analysis of the correlation between the relative systemic exposure ratio, the relative dose ratio (rat mg/kg MTD: human mg/kg maximum recommended dose (MRD)) and the dose ratio adjusted for body surface area (rat mg/meter squared (M²) MTD: human mg/M² MRD), performed in conjunction with the above described database analysis indicates that the relative systemic exposure corresponds better with dose ratios expressed in terms of body surface area rather than of body weight. When 123 compounds in the expanded FDA database were analyzed by this approach, a similar distribution of relative systemic exposures was observed.

In the selection of a relative systemic exposure ratio (AUC ratio) to apply in high dose selection, consideration was given to a ratio value that would be attainable by a reasonable proportion of compounds, that would detect known or probable human carcinogens (International Agency for Research on Cancer (IARC) 1 or 2A) and that represents an adequate margin of safety.

To address the issue of detection of known or probable human carcinogenic therapeutics, an analysis of exposure and/or dose ratios was performed on IARC class 1 and 2A therapeutics with positive rat findings. For phenacetin, sufficient rat and human pharmacokinetic data is available to estimate that a relative systemic exposure ratio of at least 15 is necessary to produce positive findings in a rat carcinogenicity study. For most of 14 LARC 1 and 2A drugs evaluated with positive carcinogenicity findings in rats, there is a lack of adequate pharmacokinetic data. For these compounds, the body surface area adjusted dose ratio was employed as a surrogate for the relative systemic exposure ratio. The results of this analysis indicated that using doses in rodents corresponding to body surface area ratios of 20 or less would identify the carcinogenic potential of these therapeutics.

As a result of the evaluations described above, a minimum systemic exposure ratio of 25 is proposed as an acceptable pharmacokinetic endpoint for high dose selection. This value was attained by approximately 25 percent of compounds tested, is high enough to detect known or probable (IARC 1, 2A) human carcinogenic drugs and represents an adequate margin of safety. Those therapeutics tested using a 25-fold or greater AUC ratio for the high dose will have exposure ratios greater than 75 percent of pharmaceuticals tested previously in carcinogenicity studies performed at the MTD.

Note 5

The rodent AUC's and metabolite profiles may be determined from separate steady state kinetic studies, as part of the subchronic toxicity studies, or dose ranging studies.

Note 6

AUC values in rodents are usually obtainable using a small number of animals (e.g. four or more time points with as few as four animals each), depending on the route of administration and the availability of data on the pharmacokinetic characteristics of the test compound.

Note 7

Equivalent analytical methods of adequate sensitivity and precision are used to determine plasma concentrations of therapeutics in rodents and humans.

Note 8

For example, when protein binding is low in both humans and rodents or when protein binding is high and the unbound fraction of drug is greater in rodents than in man, the comparison of total plasma concentration of drug is acceptable. When protein binding is high and the unbound fraction is greater in man than in rodents, the ratio of the unbound concentrations should be used.

Note 9

Human systemic exposure data may be derived from pharmacokinetic monitoring in normal volunteers and/or patients. In the absence of knowledge of the maximum recommended human daily dose, at a minimum, doses producing the desired pharmacodynamic effect in humans are used to derive the pharmacokinetic data.

Note 10

When using any new endpoint, either pharmacokinetic, pharmacodynamic, or toxicity based for high dose selection it is necessary to carefully consider, prior to carcinogenicity study initiation, if the endpoint can insure the acceptability of the carcinogenicity study. In the United States, it is considered advisable to do this by consultation with the FDA.

Dated: February 23, 1994.

Michael R. Taylor,

Deputy Commissioner for Policy.

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[Docket No. 94D-0015]

International Conference on Harmonization; Draft Guideline on the Assessment of Systemic Exposure in Toxicity Studies; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is publishing a draft guideline entitled, "Toxicokinetics: A Guidance on the Assessment of Systemic Exposure in Toxicity Studies." This guideline was prepared by the Safety Expert Working Group of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). This draft guideline is intended to help ensure that the assessment of systemic exposure in toxicity studies to support drug registration is carried out according to sound scientific principles.

DATES: Written comments by May 16, 1994.

ADDRESSES: Submit written comments on the draft guideline to the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT:

Regarding the draft guideline: Alan S. Taylor, Center for Drug Evaluation and Research (HFD-502), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-2544.

Regarding the ICH: Janet Showalter, Office of Health Affairs (HFY-50), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-1382.

SUPPLEMENTARY INFORMATION: In recent years, many important initiatives have been undertaken by regulatory authorities and industry associations to promote harmonization of regulatory requirements. FDA has participated in many meetings designed to enhance harmonization and is committed to seeking scientifically based harmonized technical procedures for pharmaceutical development. One of the goals of harmonization is to identify and then reduce differences in technical requirements for drug development.

ICH was organized to provide an opportunity for tripartite harmonization initiatives to be developed with technical input from both regulatory and industry representatives. FDA also seeks input from consumer representatives and other interested parties. Through notices such as this, FDA invites public comment on ICH initiatives that have reached the draft guideline stage. ICH is concerned with harmonization of technical requirements for the registration of pharmaceutical products among three regions: the European Union, Japan, and the United States. The six ICH sponsors are the European Commission, the European Federation of Pharmaceutical Industry Associations, the Japanese Ministry of Health and Welfare, the Japanese Pharmaceutical Manufacturers Association, FDA, and the U.S. Pharmaceutical Manufacturers Association. The ICH Secretariat, which coordinates the preparation of documentation, is provided by the International Federation of Pharmaceutical Manufacturers Associations (IFPMA).

The ICH Steering Committee includes representatives from each of the ICH sponsors and IFPMA, as well as observers from the World Health Organization, the Canadian Health Protection Branch, and the European Free Trade Area.

At a meeting held on October 27 through 29, 1993, the ICH Steering Committee agreed that the draft tripartite guideline entitled "The Assessment of Systemic Exposure in Toxicity Studies" should be made available for public comment. The draft guideline will be made available for comment by the European Commission and Japanese Ministry of Health and Welfare, as well as by FDA, in accordance with their respective consultation procedures. After analyzing the comments and revising the guideline, if appropriate, FDA will determine whether it will adopt and issue the guideline. The draft guideline discusses toxicokinetics, which is the generation of pharmacokinetic data in nonclinical toxicity studies or ancillary studies to assess exposure. The objectives of toxicokinetics are: (1) To describe the systemic exposure achieved in animals, its relationship to dose level, and the time course of the toxicity study; (2) to relate the exposure achieved in toxicity studies to toxicological findings; (3) to support the choice of species and treatment regimen in nonclinical toxicity studies; and (4) to supply information which, along with the toxicity findings, will contribute to developing additional nonclinical toxicity studies.

Guidelines are generally issued under §§ 10.85(d) and 10.90(b) (21 CFR 10.85(d) and 10.90(b)), which provide for the use of guidelines to establish procedures or standards of general applicability that are not legal requirements but that are acceptable to FDA. The agency is now in the process of considering whether to revise §§ 10.85(d) and 10.90(b). Therefore, if the agency issues this guideline in final form, the guideline would not be issued under the authority of §§ 10.85(d) and 10.90(b), and would not create or confer any rights, privileges, or benefits for or on any person, nor would it operate to bind FDA in any way.

Interested persons may, on or before May 16, 1994, submit written comments on the draft guideline to the Dockets Management Branch (address above). Two copies of any comments are to be submitted, except that individuals may submit single copies. Comments are to be identified with the docket number found in brackets in the heading of this document. The draft guideline and received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

The text of the draft guideline follows:

Toxicokinetics: A Guidance on the Assessment of Systemic Exposure in Toxicity Studies

1. Introduction

This Note for Guidance concerns toxicokinetics only with respect to the development of pharmaceutical products intended for use in human subjects¹.

In this context, toxicokinetics is defined as the generation of pharmacokinetic data, either as an integral component in the conduct of nonclinical toxicity studies or in specially designed supportive studies, in order to assess systemic exposure. These data may be used in the interpretation of toxicology findings and their relevance to clinical safety issues (see Note 1 for definitions of other terms used in this document).

The Note for Guidance has been developed in order to provide an understanding of the meaning and application of toxicokinetics and to provide guidance on developing test strategies in toxicokinetics. The guidance highlights the need to integrate pharmacokinetics into toxicity testing, which should aid in the interpretation of the toxicology findings and promote rational study design development.

Toxicokinetic measurements are normally integrated within the toxicity studies and as such are described in this document as 'concomitant toxicokinetics' (Note 1). Alternatively, data may be generated in other supportive studies conducted by mimicking the conditions of the toxicity studies.

Toxicokinetic procedures provide a means of obtaining multiple dose pharmacokinetic data in the test species, if appropriate parameters are monitored, thus avoiding duplication of such studies; optimum design in gathering the data will reduce the number of animals required.

Various components of the total nonclinical pharmacokinetics and metabolism programme may be of value in contributing to the interpretation of toxicology findings. However, the toxicokinetic data focuses on the kinetics of a new therapeutic agent under the conditions of the toxicity studies themselves.

Toxicokinetics is thus an integral part of the nonclinical testing programme; it should enhance the value of the toxicological data generated, both in terms of understanding the toxicity tests and in comparison with clinical data as part of the assessment of risk and safety in humans. Due to its integration into toxicity testing and its bridging character between nonclinical and clinical studies, the focus is primarily on the interpretation of toxicity tests and not on characterizing the basic pharmacokinetic parameters of the substance studied.

As the development of a pharmaceutical product is a dynamic process which involves continuous feed-back between nonclinical and clinical studies, no rigid *detailed* procedures for the application of toxicokinetics are recommended. It may not be necessary for toxicokinetic data to be collected in all studies and scientific judgement should dictate when such data may be useful. The need for toxicokinetic data and the extent of exposure

assessment in individual toxicity studies should be based on a flexible step-by-step approach and a case-by-case decision making process to provide sufficient information for a risk and safety assessment.

2. The Objectives of Toxicokinetics and the Parameters Which May Be Determined

The primary objective of toxicokinetics is:

- to describe the systemic exposure achieved in animals and its relationship to dose level and the time course of the toxicity study;

Secondary objectives are:

- to relate the exposure achieved in toxicity studies to toxicological findings and contribute to the assessment of the relevance of these findings to clinical safety;
- to support (Note 1) the choice of species and treatment regimen in nonclinical toxicity studies;
- to provide information which, in conjunction with the toxicity findings, contributes to the design of *subsequent* nonclinical toxicity studies.

These objectives may be achieved by the derivation of one or more pharmacokinetic parameters (Note 2) from measurements made at appropriate time points during the course of the individual studies. These measurements usually consist of plasma (or whole blood or serum) concentrations for the parent compound and/or metabolite(s) and should be selected on a case-by-case basis. Plasma (or whole blood or serum) AUC, C_{max}, and C_(time) (Note 2) are the most commonly used parameters in assessing exposure in toxicokinetic studies. For some compounds it will be more appropriate to calculate exposure based on the (plasma protein) unbound concentration.

These data may be obtained from all animals in a toxicity study, in representative subgroups, or in satellite groups (see 3.5 and Note 3).

Toxicity studies which may be usefully supported by toxicokinetic information include single and repeated dose toxicity studies, and reproductive, genotoxicity, and carcinogenicity studies. Toxicokinetic information may also be of value in assessing the implications of a proposed change in the clinical route of administration.

3. General Principles To Be Considered

3.1 Introduction

In the following paragraphs some general principles are set out which should be taken into consideration in the design of individual studies.

It should be noted that for those toxicity studies whose performance is subject to Good Laboratory Practice (GLP) the concomitant toxicokinetics should also conform to GLP Toxicokinetic studies retrospectively designed to generate specific sets of data under conditions which closely mimic those of the toxicity studies should also conform to GLP.

3.2 Quantification of exposure

The quantification of systemic exposure provides an assessment of the burden on the test species and assists in the interpretation of similarities and differences in toxicity across species, dose groups, and sexes. The exposure might be represented by plasma (serum or blood) concentrations or the AUC's of parent compound and/or metabolite(s). In some circumstances, studies may be designed to investigate tissue concentrations. When

designing the toxicity studies, the exposure and dose-dependence in humans at therapeutic dose levels (either expected or established), should be considered in order to achieve relevant exposure at various dose levels in the animal toxicity studies. The possibility that there may be species differences in the pharmacodynamics of the substance (either qualitative or quantitative) should also be taken into consideration.

Pharmacodynamic or toxicodynamic effects might also give supporting evidence of exposure or even replace pharmacokinetic parameters in some circumstances.

Toxicokinetic monitoring or profiling of the toxicity studies should establish what level of exposure has been achieved during the course of the study and may also serve to alert the toxicologist to non-linear dose related changes in exposure (Note 4) which may have occurred. Toxicokinetic information may allow better interspecies comparisons than simple dose/body-weight (or surface area) comparisons⁴.

3.3 Justification of time points for sampling

The time points for collecting body fluids in concomitant toxicokinetic studies should be as frequent as is necessary, but not so frequent as to interfere with the normal conduct of the study or to cause undue physiological stress to the animals (Note 5). In each study, the number of time points should be justified on the basis that they are adequate to estimate exposure (see 3.2). The justification should be based on kinetic data gathered from earlier toxicity studies, from pilot or dose range-finding studies, from separate studies in the same animal model or in other models allowing reliable extrapolation.

3.4 Contribution to the setting of dose levels in order to produce adequate exposure

3.4.1 Introduction

The setting of dose levels in repeat dose toxicity studies is largely governed by the toxicology findings and the pharmacodynamic responses of the test species. However, the following toxicokinetic principles may contribute to the setting of the dose levels.

3.4.2 Low dose levels

At the low dose level, preferably a no-toxic-effect dose level (Note 6), the exposure in toxicity studies (of all kinds) should normally exceed that expected or known to be attained in humans at steady state following therapeutic dose levels. There are, however, cases where this objective may not be achieved even with the maximum dose which can be administered.

3.4.3 Intermediate dose levels

Exposure at intermediate dose levels should normally represent an appropriate multiple (or fraction) of the exposure at lower (or higher) dose levels dependent upon the objectives of the toxicity study.

3.4.4 High dose levels

The high dose levels in toxicity studies will normally be determined by toxicological considerations. However, the exposure achieved at the dose levels used should be assessed.

Where toxicokinetic data indicate that absorption of a compound limits exposure to parent compound and/or metabolite(s) (Note 7), the lowest dose level of the substance

producing the maximum exposure should be accepted as the top dose level to be used (particularly when no other dose-limiting constraint applies, Note 8).

Very careful attention should be paid to the interpretation of toxicological findings in toxicity studies (of all kinds) when the dose levels chosen result in non-linear kinetics (Note 4). However, non-linear kinetics should not necessarily result in dose limitations in toxicity studies or invalidate the findings; toxicokinetics can be very helpful in assessing the relationship between dose and exposure in this situation.

3.5 Extent of exposure assessment in toxicity studies

In toxicity studies, systemic exposure should be estimated in an appropriate number of animals and dosed groups (Note 9) to provide a basis for risk assessment.

Concomitant toxicokinetics may be performed either in all or a representative proportion of the animals used in the main study or in special satellite groups (Notes 1, 3 and 5). Normally, samples for the generation of toxicokinetic data may be collected from main study animals, where large animals are involved, but satellite groups may be required for the smaller (rodent) species.

The number of animals to be used should be the minimum consistent with generating adequate toxicokinetic data. Where both male and female animals are utilised in the main study it is normal to estimate exposure in animals of both sexes unless some justification can be made for not so doing.

Toxicokinetic data are not necessarily required from studies of different duration if the dosing regimen is essentially unchanged (see also 4.3).

3.6 Complicating factors in exposure interpretation

Although estimating exposure as described above may aid in the interpretation of toxicity studies and in the comparison with human exposure, a few caveats should be noted.

Species differences in protein binding, tissue uptake, receptor properties, and metabolic profiles should be considered. For example, it may be more appropriate for some compounds to have exposure expressed as the free (unbound) concentrations. In addition, the pharmacological activity of metabolites, the toxicology of metabolites and antigenicity of biotechnology products may be complicating factors. Furthermore, it should be noted that even at relatively low plasma concentrations, high levels of the administered compound and/or metabolite(s) may occur in specific organs or tissues.

3.7 Route of administration

The toxicokinetic strategy to be adopted for the use of alternative routes of administration, for example by inhalation, topical, or parenteral delivery, should be based on the pharmacokinetic properties of the substance administered by the intended route.

It sometimes happens that a proposal is made to adopt a new clinical route of administration for a pharmaceutical product for example, a product initially developed as an oral formulation may subsequently be developed for intravenous administration. In this context, it will be necessary to ascertain whether changing the clinical route will significantly reduce the safety margin.

This process may include a comparison of the systemic exposure to the compound and its relevant metabolite(s) (plasma AUC and C_{max}) in humans generated by the ex-

isting and proposed routes of administration. If the new route results in increased AUC and/or C_{max}, or a change in metabolic route, the continuing assurance of safety from animal toxicology and kinetics should be reconsidered. If exposure is not substantially greater, or different, by the proposed new route compared to that for the existing route(s) then additional nonclinical toxicity studies may focus on local toxicity.

3.8 Determination of metabolites

A primary objective of toxicokinetics is to describe the systemic exposure to the administered compound achieved in the toxicology species. However, there may be circumstances when measurement of metabolite concentrations in plasma or other body fluids is especially important in the conduct of toxicokinetics:

- When the administered compound acts as a 'pro-drug' and the delivered metabolite is acknowledged to be the primary active entity
- When the compound is metabolised to a pharmacologically or toxicologically active metabolite which would make a significant contribution to the pharmacological or toxicological response, in addition to the compound itself (Note 10).
- When the administered compound is very extensively metabolized and the measurement of plasma or tissue concentrations of a major metabolite is the only practical means of estimating exposure following administration of the compound in toxicity studies (Note 11).

3.9 Statistical evaluation of data

The data should allow a representative assessment of the exposure. However, because large intra- and interindividual variation of kinetic parameters may occur and small numbers of animals are involved in generating toxicokinetic data, a high level of precision in terms of statistics is *not* normally possible or required. Consideration should be given to the calculation of mean or median values and estimates of variability, but in some cases the data for individual animals may be more important than a refined statistical analysis of group data.

3.10 Analytical methods

Integration of pharmacokinetics into toxicity testing implies early development of analytical methods for which the choice of analytes and matrices should be continually reviewed as information is gathered on metabolism and species differences.

The analytical methods to be used in toxicokinetic studies should be specific for the entity to be measured and of an adequate accuracy and precision⁶. The limit of quantification should be adequate for the measurement of the range of concentrations anticipated to occur in the generation of the toxicokinetic data.

The choice of analyte and the matrix to be assayed (biological fluids or tissue) should be stated and possible interference by endogenous components in each type of sample (from each species) should be investigated. Plasma or whole blood are normally the matrices of choice for toxicokinetic studies.

If the drug substance is a racemate or some other mixture of enantiomers, additional justification should be made for the choice of the analyte [racemate or enantiomer(s)].

The analyte and matrix assayed in nonclinical studies should ideally be the same as in clinical studies. If different assay methods are used in nonclinical and clinical studies they should all be suitably validated⁶.

3.11 Reporting

A rationale for the toxicokinetic policy adopted should be reported either in the toxicity study report or in a separate report. A comprehensive account of the toxicokinetic data generated, together with an evaluation of the results and of the implications for the interpretation of the toxicology findings should be given.

An outline of the analytical method should be reported or referenced. In addition, a rationale for the choice of the matrix analysed and the analyte measured (see 3.8 and 3.10) should be given.

4. Toxicokinetics in the Various Areas of Toxicity Testing-Specific Aspects

4.1 Introduction

Based on the principles of toxicokinetics outlined above, the following specific considerations refer to individual areas of toxicity testing. The frequency of exposure monitoring or profiling may be extended or reduced where necessary.

It may be appropriate to take samples from individual animals on a study where this may help in the interpretation of the toxicology findings for these animals.

4.2 Single-dose toxicity studies

These studies are often performed in a very early phase of development before a bioanalytical method has been developed and toxicokinetic monitoring of these studies is therefore not normally possible. Plasma samples may be taken in such studies and stored for later analysis; appropriate stability data for the analyte in the matrix sampled would then be needed.

Alternatively, additional toxicokinetic studies may be carried out *after* completion of a single dose toxicity study in order to respond to specific questions which may arise from the study.

Results from single dose kinetic studies may help in the choice of formulation and in the prediction of rate and duration of exposure during a dosing interval. This may assist in the selection of appropriate dose levels for use in later studies.

4.3 Repeated dose toxicity studies

The treatment regimen (Note 12) and species should be selected whenever possible with regard to pharmacodynamic and pharmacokinetic principles. This may not be achievable for the very first studies, at a time when neither animal nor human pharmacokinetic data are normally available.

Toxicokinetics should be incorporated appropriately into the design of the studies. It may consist of exposure profiling or monitoring (Note 1) at appropriate dose levels at the start and towards the end of the treatment period of the first repeat dose study (Note 13). The procedure adopted for later studies will depend on the results from the first study and on any changes in the proposed treatment regimen. Monitoring or profiling may be extended or reduced, or modified for specific compounds where problems have arisen in the interpretation of earlier toxicity studies.

4.4 Genotoxicity studies

For negative results of *in vivo* genotoxicity studies, it may be appropriate to have demonstrated systemic exposure in the species used or to have characterized exposure in the indicator tissue⁷.

4.5 Carcinogenicity (*Oncogenicity*) studies

4.5.1 *Sighting or dose-ranging studies*

Appropriate monitoring or profiling of these studies should be undertaken in order to generate toxicokinetic data which may assist in the design of the main studies (see 4.5.2). Particular attention should be paid to species and strains which have not been included in earlier toxicity studies and to the use of routes or methods of administration which are being used for the first time.

Toxicokinetic data may assist in the selection of dose levels in the light of information about clinical exposure and in the event that non-linear kinetics (Note 4) may complicate the interpretation of the study. Particular attention should be paid to the establishment of appropriate toxicokinetic data when administration is to be in the diet (Note 14).

It is recommended that dose levels in oncogenicity studies generate a range of systemic exposure values that exceed the maximum therapeutic exposure for humans by varying multiples. However, it is recognized that this idealized selection of dose levels may be confounded by unavoidable species-specific problems. Thus, the emphasis of this guidance is on the need to estimate systemic exposure, to parent compound and/or metabolite(s) at appropriate dose levels and at various stages of an oncogenicity study, so that the findings of the study may be considered in the perspective of comparative exposure for the animal model and humans.

In practice, the 'Maximum Tolerated Dose' (MTD) has been used, whenever possible, as the top dose level in these studies. However, it has been suggested⁸ that it may be acceptable to select a high dose level based on consideration of the kinetics in humans and in the test species.

For nongenotoxic compounds of comparatively low general toxicity, in addition to a toxicity-based endpoint (MTD) which remains acceptable, it has been proposed⁹ reasonable to define a level of animal exposure that would be considered sufficiently great, compared to human exposure, to provide reassurance of an adequate test of carcinogenicity. It is considered important to compare exposure rather than administered dose because the latter does not take into account inter-species differences in pharmacokinetics⁹.

4.5.2 *The main studies*

The treatment regimen and species and strain selection should, as far as is feasible, be determined with regard to the available pharmacokinetic and toxicokinetic information. In practice, the vast majority of these studies are conducted in the rat and mouse. Reassurance should be sought from the toxicokinetic data that the exposure level in the chosen species is consistent with the results from the dose ranging studies.

Concomitant toxicokinetics may be confined to monitoring exposure at appropriate dose levels at a number of stages in the study. Appropriate stages may be early in the study, and after prolonged treatment, for example, at one year. It is not considered necessary to monitor exposure beyond one year in these studies. The design for each test should be selected on a compound by compound basis utilizing data gathered from earlier studies (see 4.5.1).

4.6 Reproductive toxicity studies

4.6.1 Introduction

It is preferable to have some information on pharmacokinetics before initiating reproduction studies, since this may suggest the need to adjust the choice of species, study design, and dosing schedules. At this time, the information need not be sophisticated or derived from pregnant or lactating animals¹⁰. At the time of study evaluation, further information on pharmacokinetics in pregnant or lactating animals may be necessary depending on the results obtained¹⁰.

The limitation of exposure in reproductive toxicity is usually governed by maternal toxicity. Thus, while toxicokinetic monitoring in reproductive toxicity studies may be valuable in some instances, especially with compounds with low toxicity, such data are not generally necessary for all compounds.

Where appropriate, toxicokinetic principles should be applied to determine the exposures achieved in the different stages of the reproduction toxicity studies. A satellite group of female animals may be used to collect the toxicokinetic data.

4.6.2 Fertility studies

The general principles for repeated dose toxicity studies apply (see 4.3). The need to monitor these studies will depend on the dosing regimen used and the information already available from earlier studies in the selected species.

4.6.3 Studies in pregnant and lactating animals

The treatment regimen during the exposure period should be selected on the basis of the toxicological findings and on pharmacokinetic and toxicokinetic principles.

Toxicokinetics may involve exposure assessment of dams, embryos, fetuses, or newborn at specified days (Note 15). Secretion in milk may be assessed to define its role in the exposure of newborn. In some situations, additional studies may be necessary or appropriate in order to study embryo/fetal transfer and secretion in milk.

Consideration should be given to the possibility that pharmacokinetics may differ in pregnant and non-pregnant animals.

Consideration should be given to the interpretation of reproductive toxicity tests in species in which placental transfer of the substance cannot be demonstrated (Note 16).

5. Supplementary Notes

Note 1 Definitions of expressions appearing in this “Note for Guidance”:

Analyte: the chemical entity assayed in biological samples.

Concomitant toxicokinetics: toxicokinetic measurements performed in the toxicity study animals, either in all or in representative subgroups or in satellite groups.

Exposure: exposure is represented by pharmacokinetic parameters demonstrating the local and systemic burden on the test species with the test compound and/or its metabolites. The area under the plasma level concentration-time curve (AUC) and/or the measurement of plasma concentrations at the expected peak-concentration time C_{max} , or at some other selected time $C_{(time)}$, are the most commonly used parameters. Others might be more appropriate in particular cases.

Monitor: to take a small number of blood samples (say 1–3) during a dosing interval to estimate $C_{(time)}$ or C_{max} .

Profile: to take (say) 4–8 blood samples during a dosing interval to make an estimate of $C_{\max}$ and/or $C_{(\text{time})}$ and area under the plasma concentration-time curve (AUC).

Satellite groups: groups of animals included in the design and conduct of the toxicity study and housed with the main-study animals, but used primarily for toxicokinetics.

Support: in the context of a toxicity study—to ratify or confirm the design of a toxicity study with respect to pharmacokinetic and metabolic principles. This process may include two separate steps:

a) confirmation using toxicokinetic principles that the animals on a study were exposed to appropriate systemic levels of the administered compound (see 3.4) and/or its metabolite(s).

b) confirmation that the metabolic profile in the species used was acceptable; data to support b) will normally be derived from metabolism studies in animals and in humans.

Validate: in the context of an analytical method—to establish the accuracy, precision, reproducibility, response function and the specificity of the analytical method with reference to the biological matrix to be examined and the analyte to be quantified⁶.

Note 2 Symbols and definitions according to ‘Manual of Symbols, Equations and Definitions in Pharmacokinetics’, Committee for Pharmacokinetic Nomenclature of the American College of Clinical Pharmacology, Philadelphia, PA, May 1982:

$C_{\max}$ —Maximum (peak) plasma concentration

$C_{(\text{time})}$ —Plasma concentration at a specified time after administration of a given dose

$t_{\max}$ —Time to reach peak or maximum concentration following administration

$AUC_{(0-1)}$ —Area under concentration-time curve from zero to time t . It should be noted that $AUC_{(0-\infty)}$ is a special case of $AUC_{(0-1)}$.

Other measurements, for example urinary excretion, may be more appropriate for some compounds. Other derived parameters, for example bioavailability, half-life, fraction of unbound drug, and volume of distribution may be of value in interpreting toxicokinetic data. Thus, the selection of parameters and time points has to be made on a case-by-case basis considering the general principles as outlined in Section 3.

Note 3 Satellite groups (Note 1) to toxicity studies should be housed in conditions identical to those provided for the main test animals and be subject to the same dosing procedures and animal husbandry procedures.

Note 4 Increases in exposure may arise unexpectedly as a result of non-linear kinetics¹¹ due to saturation of a clearance process. Increasing exposure may also occur during the course of a study for those compounds which have a particularly long plasma half-life. Careful attention should also be paid to compounds which achieve high plasma $C_{\max}$ values over comparatively short time periods within the dosing interval. Conversely, unexpectedly low exposure may occur during a study as a result of auto-induction of metabolic enzymes.

Note 5 If samples are taken from main study animals it should be considered whether samples should be taken from *all* the dosed animals and the controls in order to treat all animals on the study in the same way, or whether samples should be taken from representative subgroups of the same size.

Note 6 In this context, a ‘no-toxic-effect dose level’ (deemed to be the same as ‘no-observed-adverse-effect dose level’) is defined as a dose level at which some pharmacological response may be observed, but at which no adverse effect is found.

Note 7 In these circumstances it should be established that absorption is the rate

limiting step and that limitations in exposure to the administered substance are not due to an increased clearance by metabolism.

Note 8 The limits placed on acceptable volumes which can be administered orally to animals may constrain the dose levels achievable for comparatively non-toxic compounds administered as solutions or suspensions.

Note 9 It is often considered unnecessary to assay samples from control groups, but samples may be collected and then assayed if it is deemed that this may help in the interpretation of the toxicity findings, or in the validation of the assay method.

Note 10 Measurement of metabolite concentrations may be especially important when documentation of exposure to human metabolite(s) is needed in the nonclinical toxicity studies in order to demonstrate adequate toxicity testing of these metabolites⁵.

Note 11 It is recognized that measurement of metabolite(s) as a part of toxicokinetic evaluation serves only to assess exposure and cannot account for possible reactive intermediate metabolites¹².

Note 12 Treatment regimen encompasses dosage, formulation, route of administration and dosing frequency.

Note 13 The first repeat dose study incorporating toxicokinetic data for each species is normally of 14 days' duration or longer.

Note 14 Additional studies may be necessary in order to compare exposure to the compound administered in diet and by gavage or by routes different from the intended clinical route.

Note 15 Separate pharmacokinetic studies may be needed in order to establish the pharmacokinetic profile in species and strains selected for reproductive toxicity studies which have not been previously selected for general toxicity studies. It should be noted that while it is important to consider the transfer of substances entering the embryo-fetal compartment, fetal exposure is the parameter which is most often assessed in practice and expressed as 'placental transfer'.

Note 16 For practical reasons, it is normally accepted that placental transfer has not been demonstrated if the concentration in the whole fetus does not exceed 1% of the maternal plasma concentration.

7. References

1 Design of Toxicokinetic Studies, Smith D. A., Humphrey M. J., and Charuel, *Xenobiotica*, 1990, Vol. 20, No. 11. 1187–1199.

2 Food and Drug Administration, Department of Health and Human Services, Statement dated June 9th 1993.

3 Commission of the European Communities, Statement on Applicability of Good Laboratory Practice (III/3824/92).

4 Opportunities for Integration of Pharmacokinetics, Pharmacodynamics, and Toxicokinetics in Rational Drug Development, Peck C. C. et al., *Pharmaceutical Research*, 1992, Vol. 9, No. 6, 826–833.

5 Proceedings of The First International Conference on Harmonization, Brussels 1991. Ed: D'Arcy, P. F. and Harron, D. W. G. (1992), page 188.

6 Analytical methods validation: Bioavailability, Bioequivalence and Pharmacokinetic Studies, Shah, V. P. et al., *European Journal of Drug Metabolism and Pharmacokinetics*, 1991, Vol. 16, No. 4, 249–255.

7 ICH Joint Position Paper: Genotoxicity, 1993.

8 Proceedings of The First International Conference on Harmonization, Brussels 1991. Ed: D'Arcy, P. F. and Harron, D. W. G. (1992), pages 185 and 331.

9 ICH Position Paper: 'High Dose Selection for Carcinogenicity Studies', 1993.

10 ICH Tripartite Guideline: 'Guideline on Detection of Toxicity to Reproduction for Medicinal Products', 1993.

11 Gibaldi M. and Perrier D., 'Pharmacokinetics' Second Edition, Chapter 7, Marcel Dekker Inc., New York (1982).

12 What is an appropriate measure of exposure when testing drugs for carcinogenicity in rodents? Monro, A., *Toxicology and Applied Pharmacology*, 1992, 112, 171–181.

Dated: February 23, 1994.

Michael R. Taylor,

Deputy Commissioner for Policy.

[FR Doc. 94–4569 Filed 2–24–94; 1:35 pm]

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 211

[Docket No. 94N–0421]

RIN 0905–AE63

Current Good Manufacturing Practice for Finished Pharmaceuticals; Positron Emission Tomography

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to amend its regulations to permit manufacturers of positron emission tomography (PET) radiopharmaceuticals to apply to the agency for approval of an exception or alternative to the requirements of the current good manufacturing practice (CGMP) regulations. This action is intended to relieve PET manufacturers, nearly all of whom are small entities, from regulations that might result in unsafe handling of PET radiopharmaceuticals, that are inapplicable or inappropriate, or that otherwise do not enhance safety or quality in the manufacture of PET radiopharmaceuticals.

DATES: Written comments by March 29, 1995. FDA proposes that any final rule that may issue based on this proposal become effective on its date of publication in the **Federal Register**.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA–305), Food and Drug Administration, rm. 1–23, 12420 Parklawn Dr., Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: John W. Levchuk, Center for Drug Evalu-

ation and Research (HFD-322), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301-594-0095.

SUPPLEMENTARY INFORMATION:

I. Introduction

PET is a diagnostic imaging modality consisting of onsite production of radionuclides that are intravenously injected into patients for diagnostic purposes. The potential usefulness of a PET radiopharmaceutical is based upon the product's interaction with a biochemical process in the body. For example, the product may be substituted for glucose in anaerobic glycolysis, theoretically localizing in ischemic tissues where glucose metabolism is the predominant energy source (epileptic foci, acute vascular insufficiency states).

The manufacture of PET radiopharmaceuticals consists of a process that takes place within a few hours. A target material is irradiated by a cyclotron; chemical synthesis takes place in a programmed, automated apparatus; and the final solution is compounded and filled. The biological distribution of a PET radiopharmaceutical in the body is monitored by a positron tomograph, or PET scanner, which detects the photons emitted as a result of the radioactive decay of the PET radiopharmaceutical.

PET manufacturing procedures differ in a number of important ways from those associated with the manufacture of conventional drug products:

- Because of the short half-lives of PET radiopharmaceuticals (some of which are only minutes long), PET facilities generally manufacture the products in response to daily demand for a relatively small number of patients.
- Manufacturing is typically done on a small scale and only a few lots are produced each day. Thus, the daily production of a PET facility is normally handled by few employees, sometimes by one production operator and a part-time support person.
- PET radiopharmaceuticals must be administered to patients in a short-period of time because of the brief half-lives of the products. Any prolonged manufacturing time or testing or release delays would reduce the useful clinical life of the product.
- Unlike most pharmaceuticals, PET radiopharmaceuticals usually do not enter a general drug distribution chain. An entire lot (one vial) is usually distributed directly from the PET facility to a single medical department, to a physician for administration to patients, to a radiopharmacy for dispensing, or to another site close to the PET facility. The receiving facilities are in a geographic proximity that will allow for receipt and use within the product's half-life parameters.

The agency believes that there are fundamental principles of the CGMP regulations that need to be applied to drug manufacturing processes, including those for PET radiopharmaceuticals, to ensure the safety and efficacy of the finished products. However, as just noted, certain features are unique to the manufacture of PET products. Part 211 (21 CFR part 211), which is primarily directed to the regulation of conventional drug products, contains requirements and specific language which might result in unsafe handling of PET radiopharmaceuticals, are inapplicable or inappropriate, or which otherwise do not enhance drug product quality in the manufacture of PET radiopharmaceuticals.

FDA is therefore proposing to amend its regulations to permit manufacturers of PET radiopharmaceuticals to apply to the agency for approval of an exception or alternative to the requirements of part 211 as they apply to the manufacture of PET radiopharmaceuti-

icals. A request for an exception or alternative must contain either an explanation why compliance with a particular requirement of the CGMP regulations is unnecessary or cannot be achieved, or a description of alternative procedures or controls that satisfy the purpose of the CGMP requirement. Both of these must include all necessary supporting data. Alternatively, the request may include other information justifying an exception or alternative. The request for an exception or alternative may be approved by the agency if it is determined that the requestor's compliance with the CGMP requirement is unnecessary to provide suitable assurance that the drug meets the requirements of the act as to safety and it has the identity and strength and meets the quality and purity characteristics that it purports or is represented to possess, or if compliance with the requirement cannot be achieved. In addition, the request for an exception or alternative may be approved if the requestor's alternative procedures or controls satisfy the purpose of the CGMP requirement, or if the requestor's submission otherwise justifies an exception or alternative. The agency may withdraw approval of an exception or alternative if it finds, on the basis of new information, that the criteria for approval are no longer met. Such withdrawal will be accomplished by providing written notice, and the reasons for the action, to the original requestor.

The agency will also periodically provide guidance to the industry on the application of the CGMP regulations to PET radiopharmaceuticals.

Elsewhere in this issue of the Federal Register, FDA is publishing: (1) A notice of availability of a draft guideline to assist persons in determining whether certain manufacturing practices, procedures, and facilities used for PET radiopharmaceuticals are in compliance with FDA's CGMP regulations; and (2) a notice of a public workshop and FDA guidance on the regulation of PET radiopharmaceuticals.

FDA is requesting written comments within 30 days after the date of publication of this proposed rule. In addition, FDA is proposing that any final rule that may publish as a result of this proposal become effective on its date of publication in the **Federal Register**. The proposed rule would permit manufacturers of PET radiopharmaceuticals to apply to FDA for approval of an exception or alternative to the requirements of the CGMP regulations. Accordingly, the proposed rule, if finalized, is a substantive rule which, in the discretion of the agency, grants or recognizes an exemption or relieves a restriction. (See 5 U.S.C. 553(d)(1) and 21 CFR 10.40(c)(4)(i).) In addition, the Commissioner of Food and Drugs finds good cause under 21 CFR 10.40(a)(2) for providing 30 days for comments instead of 60 days and under 5 U.S.C. 553(d)(3) and 21 CFR 10.40(c)(4)(ii) for making a final rule based on this proposal effective upon its publication in the **Federal Register**. The manufacturing process for PET radiopharmaceuticals is sufficiently different from that of other regulated products that application of certain CGMP requirements to PET radiopharmaceuticals is impractical. Because PET radiopharmaceuticals are already in use, a longer comment period or a later effective date may delay FDA approval or hinder appropriate application of CGMP regulations to PET radiopharmaceuticals, that are necessary to protect the integrity of the drug manufacturing process.

II. Request for Comments

Interested persons may, on or before March 29, 1995, submit to the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857, written comments regarding this proposal. Two copies of any

comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

III. Environmental Impact

The agency has determined under 21 CFR 25.24(a)(8) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

IV. Analysis of Impacts

FDA has examined the impacts of the proposed rule under Executive Order 12866 and the Regulatory Flexibility Act (Pub. L. 96–354). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The agency believes that this proposed rule is consistent with the regulatory philosophy and principles identified in the Executive Order. In addition, the proposed rule is not a significant regulatory action as defined by the Executive Order and so is not subject to review under the Executive Order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. The agency certifies that the proposed rule will not have a significant impact on a substantial number of small entities. Therefore, under the Regulatory Flexibility Act, no further analysis is required.

For the reasons explained above, FDA proposes that any final rule based on this proposal become effective on the date of publication in the Federal Register.

V. Paperwork Reduction Act of 1980

This proposed rule contains information collections that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1980. The title, description, and respondent description of the information collection are shown below with an estimate of the annual reporting and recordkeeping burden. Included in the estimate is the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information.

ESTIMATED ANNUAL REPORTING BURDEN:					
Section	Number of Respondents	No. of Responses Per Respondents	Total Annual Responses	Hours Per Response	Total Hours
21 CFR					
211.1(d)	60	1	60	4	240

Title: Current Good Manufacturing Practice for Finished Pharmaceuticals: Positron Emission Tomography

Description: The proposal would permit manufacturers of PET products to apply to the agency for approval of an exception or alternative to the requirements of the CGMP regulations. The regulation is intended to relieve PET manufacturers, nearly all of whom are small entities, from regulations that might result in unsafe handling of PET radiopharmaceuticals, that are inapplicable or inappropriate, or that otherwise do not enhance safety or quality in the manufacture of PET radiopharmaceuticals.

Description of Respondents: Businesses; small businesses.

We have submitted a copy of this proposed rule to OMB for its review of these information collections. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to the agency official designated for this purpose whose name appears in this preamble, and to the Office of Information and Regulatory Affairs, OMB, Washington, D.C. 20503.

List of Subjects in 21 CFR Part 211

Drugs, Labeling, Laboratories, Packaging and containers, Prescription drugs, Reporting and recordkeeping requirements, Warehouses.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR part 211 be amended as follows:

PART 211—CURRENT GOOD MANUFACTURING PRACTICE FOR FINISHED PHARMACEUTICALS

1. The authority citation for 21 CFR part 211 continues to read as follows:

Authority: Secs. 201, 501, 502, 505, 506, 507, 512, 701, 704 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 351, 352, 355, 356, 357, 360b, 371, 374).

2. Section 211.1 is amended by adding new paragraph (d) to read as follows:

§ 211.1 Scope.

* * * * *

(d) The Director of the Center for Drug Evaluation and Research or the Director of the Office of Compliance, Center for Drug Evaluation and Research, may approve an exception or alternative to any application of this part to the manufacture of positron emission tomography (PET) radiopharmaceuticals. Requests for such exceptions or alternatives should ordinarily be made in writing. However, in certain circumstances, such requests may be made orally and permission may be granted orally. Oral requests and oral approvals must be followed by written requests and written approvals. Approval of a request for an exception or alternative must be obtained from either specified Director prior to the use of any affected PET radiopharmaceutical.

(1) A request for an exception or alternative is required to contain one of the following:

(i) An explanation, with supporting data as necessary, why compliance with a particular requirement of this part is unnecessary or cannot be achieved;

(ii) A description, with supporting data as necessary, of alternative procedures or controls that satisfy the purpose of the requirement; or

(iii) Other information justifying an exception or alternative.

(2) The Director may approve a request for an exception or alternative if the Director finds one of the following:

(i) The requestor's compliance with the requirement is unnecessary to provide suitable assurance that the drug meets the requirements of the act as to safety, and has the identity and strength and meets the quality and purity characteristics that it purports or is represented to possess, or compliance with the requirement cannot be achieved;

(ii) The requestor's alternative procedures or controls satisfy the purpose of the requirement; or

(iii) The requestor's submission otherwise justifies an exception or alternative.

(3) The Director may withdraw approval of an exception or alternative if the Director finds, on the basis of new information, that the criteria for approval in paragraph (d)(2) of this section are no longer met. Withdrawal of approval shall be accomplished by providing written notice of such withdrawal, and the reasons for the withdrawal, to the original requestor.

Dated: February 17, 1995.

William B. Schultz,

Deputy Commissioner for Policy.

[FR Doc. 95-4690 Filed 2-24-95; 8:45 am]

BILLING CODE 4160-01-F

[Docket No. 94D-0422]

Draft Guideline on the Manufacture of Positron Emission Tomography Radiopharmaceutical Drug Products; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing the availability of a draft guideline entitled "Draft Guideline on the Manufacture of Positron Emission Tomographic (PET) Drug Products" prepared by FDA's Center for Drug Evaluation and Research (CDER). The draft guideline is intended to assist persons in determining whether certain manufacturing practices, procedures, and facilities used in the small-scale production of liquid injectable radiopharmaceutical drug products used for positron emission tomography (PET radiopharmaceuticals) are in compliance with FDA's current good manufacturing practice (CGMP) regulations for finished pharmaceuticals.

DATES: Written comments by May 30, 1995.

ADDRESSES: Submit written requests for single copies of the draft guideline entitled "Draft Guideline on the Manufacture of Positron Emission Tomographic (PET) Drug Products" to the CDER Executive Secretariat Staff (HFD-8), Center for Drug Evaluation and Research, Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855. Send two self-addressed adhesive labels to assist that office in processing your requests. Submit written comments on the draft guideline to the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857. Requests and comments should be identified with the docket number found in brackets in the heading of this document. A copy of the draft guideline and received comments are available for public examination in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

FOR FURTHER INFORMATION CONTACT: John W. Levchuk, Center for Drug Evaluation and Research (HFD-322), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301-594-0095.

SUPPLEMENTARY INFORMATION: FDA is announcing the availability of a draft guideline entitled "Draft Guideline on the Manufacture of Positron Emission Tomographic (PET) Drug Products." PET is a diagnostic imaging modality consisting of onsite production of radionuclides that are intravenously injected into patients for diagnostic purposes. The potential usefulness of a PET radiopharmaceutical is based upon the product's interaction with a biochemical process in the body. For example, the product may be substituted for glucose in anaerobic glycolysis, theoretically localizing in ischemic tissues where glucose metabolism is the predominant energy source (epileptic foci, acute vascular insufficiency states).

The manufacture of PET radiopharmaceuticals consists of a process that takes place within a few hours. A target material is irradiated by a cyclotron; chemical synthesis takes place in a programmed, automated apparatus; and the final solution is compounded and filled. The biological distribution of a PET radiopharmaceutical in the body is monitored by a positron tomograph, or PET scanner, which detects the photons emitted as a result of the radioactive decay of the PET radiopharmaceutical. Because of their short half-lives, PET radiopharmaceuticals are characteristically manufactured in PET centers in response to daily demand for relatively few patients. PET centers are usually located in medical centers.

PET manufacturing procedures differ in a number of important ways from those associated with the manufacture of conventional drug products, mainly due to the short half-lives involved:

1. A maximum of only a few lots are manufactured per day, with one lot equalling one multiple-dose vial. This is administered to the patient usually within a matter of hours. Prolonged manufacturing time significantly erodes the useful clinical life of PET radiopharmaceuticals.

2. The quantities of radioactive active ingredients contained in each lot of a PET radiopharmaceutical generally vary from nanogram to milligram amounts, depending upon various product parameters.

3. Because one lot equals one multiple-dose vial containing a homogeneous solution of a PET product (e.g., 2-deoxy-2 [^{18}F] fluoro-D-glucose), results from end-product testing of samples drawn from the single vial have the maximum possible probability of being representative of all the doses administered to patients from that vial, barring sampling or testing error.

4. An entire lot may be administered to one or several patients, depending upon the activity remaining in the container at the time of administration. Consequently, the administration of the entire quantity of a lot to a single patient should be anticipated for every lot manufactured. This is an important consideration when establishing the testing limits for certain attributes such as endotoxins and impurities.

5. PET radiopharmaceuticals usually do not enter a general drug distribution chain. Rather, the entire lot (one vial) is usually distributed directly from the PET center either to a single medical department or physician for administration to patients or to a radiopharmacy for dispensing. Distribution may occur to other centers when the geographic proximity will allow for distribution and use within the drug product's half-life parameters.

Conventional compliance with CGMP regulations would be expected where special

characteristics such as those listed above do not exist; for example, in large-scale PET operations. Elsewhere in this issue of the **Federal Register**, FDA is publishing (1) A proposed rule that would authorize the Director, CDER, or the Director, Office of Compliance, CDER, to approve exceptions or alternatives to the application of the provisions of 21 CFR part 211 to the manufacture of PET radiopharmaceuticals, and (2) a notice of a public workshop and FDA guidance on the regulation of PET radiopharmaceuticals.

The guideline entitled “Draft Guideline on the Manufacture of Positron Emission Tomographic (PET) Drug Products” discusses, generally, quality control units, personnel qualifications, staffing, buildings and facilities, equipment, components, containers, closures, production and process controls, packaging and labeling control, holding and distribution, testing and release for distribution, stability testing and expiration dating, reserve samples, yields, second-person checks, and reports and records.

FDA is making this draft guideline available for public comment before issuing a final guideline. If, following the receipt of comments, the agency concludes that the draft guideline will assist persons in determining whether manufacturing practices used in the small-scale production of liquid injectable PET radiopharmaceuticals are in compliance with FDA’s CGMP regulations for finished pharmaceuticals, then the agency will prepare a final guideline and will announce its availability in the **Federal Register**.

Guidelines are generally issued under § 10.90(b) (21 CFR 10.90(b)), which provides for the use of guidelines to state procedures or standards of general applicability that are not legal requirements but are acceptable to FDA. The agency is now in the process of revising § 10.90(b). Therefore, if the agency makes the guideline final, the guideline would not be issued under the authority of current § 10.90(b), and would not create or confer any rights, privileges, or benefits for or on any person, nor would it operate to bind FDA in any way.

Interested persons may, on or before May 30, 1995, submit to the Dockets Management Branch (address above) written comments on the draft guideline. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. The draft guideline and received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

Dated: February 17, 1995.
William B. Schultz,
Deputy Commissioner for Policy.
[FR Doc. 95-4689 Filed 2-24-95; 8:45 am]
BILLING CODE 4160-01-F

[Docket No. 93N-0005]
Regulation of Positron Emission Tomography Radiopharmaceutical Drug Products; Guidance; Public Workshop
AGENCY: Food and Drug Administration, HHS.
ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is publishing guidance on the regulation of positron emission tomography (PET) radiopharmaceutical drug products. FDA has developed this guidance to make clear the regulatory approach designed to help

ensure the safe and effective use of these products. The agency is also announcing a public workshop to facilitate an understanding of regulatory requirements regarding these products. DATES: The public workshop will be held on March 21, 1995, 8:30 a.m. to 4 p.m. Registration will be between 8 a.m. and 8:30 a.m. Due to limited space, interested persons must preregister before March 7, 1995, by telephoning the contact person listed below. Interested persons may submit data, information, or views on this subject to the Dockets Management Branch (address below).

ADDRESSES: The public workshop will be held at the Parklawn Bldg., conference rooms G and H, 5600 Fishers Lane, Rockville, MD 20857. Written data, information, or views regarding the workshop may be submitted to the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: John W. Levchuk, Center for Drug Evaluation and Research (HFD-322), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301-594-0095.

SUPPLEMENTARY INFORMATION:

I. Background

PET is a diagnostic imaging modality consisting of onsite production of radionuclides that are usually intravenously injected into patients for diagnostic purposes. The potential usefulness of a PET radiopharmaceutical is based upon the product's interaction with a biochemical process in the body. For example, the product may be substituted for glucose in anaerobic glycolysis, theoretically localizing in ischemic tissues (epileptic foci, acute vascular insufficiency states) where glucose metabolism is the predominant energy source.

The manufacture of PET radiopharmaceuticals consists of a process that takes place within a few hours. A target material is irradiated in a cyclotron; chemical synthesis takes place in a programmed, automated apparatus; and the final solution is prepared. The biological distribution of a PET radiopharmaceutical in the body is monitored by a positron tomograph, or PET scanner, which detects the photons emitted as a result of the radioactive decay of the PET radiopharmaceutical.

Currently, there are two FDA approved PET radiopharmaceuticals: Rubidium-82 (rubidium chloride ($^{82}\text{Rb}[\text{RbCl}]$)) and fludeoxyglucose ($^{18}\text{-F-FDG}$). At present, most investigational PET radionuclides are manufactured by cyclotrons at PET facilities, which generally are located at major teaching hospitals or their adjacent universities. Because PET radiopharmaceuticals contain positron emitting isotopes that have relatively short half-lives (minutes to hours), they are manufactured near the site of administration to patients. Products may be distributed to other institutions when the geographic proximity of these locations will allow for distribution and use within the product's half-life parameters.

The development of PET radiopharmaceuticals has increased considerably over the past several years. As this technology has advanced, questions have been raised about the most appropriate approach to regulation of PET radiopharmaceuticals. FDA held a public hearing on March 5, 1993, to receive information and views on this issue from interested groups and individuals. The docket established for the receipt of comments (Docket No. 93N-0005) remained open for an additional 2 weeks after the hearing. Additionally, FDA has received several citizen petitions on PET radiopharmaceuticals to which it will be directly responding.

Having considered the available information, including that presented to the agency

at the hearing and in written materials, FDA has concluded that radiopharmaceuticals should be regulated under the drug provisions of the Federal Food, Drug, and Cosmetic Act (the act). Under section 501(a)(2)(B) of the act (21 U.S.C. 351(a)(2)(B)), drugs are considered adulterated unless manufactured in conformity with current good manufacturing practice (CGMP). Because of unique features of PET radiopharmaceuticals, the applicability of certain requirements in the CGMP regulations for finished pharmaceuticals (part 211 (21 CFR part 211)) to PET radiopharmaceuticals may differ from the applicability of these requirements to drugs produced through traditional manufacturing methods. Consequently, elsewhere in this issue of the **Federal Register**, FDA is publishing a proposed rule that would authorize the Director of the Center for Drug Evaluation and Research (CDER) or the Director of the Office of Compliance, CDER, to approve exceptions or alternatives to the application of the provisions of part 211 to the manufacture of PET radiopharmaceuticals.

In order to assist manufacturers in complying with applicable CGMP requirements, FDA has also developed a "Draft Guideline on the Manufacture of Positron Emission Tomographic (PET) Drug Products." A notice of availability of this draft guideline, on which the agency is inviting comments, is also published elsewhere in this issue of the **Federal Register**.

Under section 505 of the act (21 U.S.C. 355), "new drugs," such as radiopharmaceuticals, must be the subjects of approved new drug applications (NDA's) or abbreviated new drug applications (ANDA's) before marketing. In order to be approved, the products must be shown to be safe and effective for their intended uses through adequate and well-controlled studies (21 U.S.C. 355(d)). Investigational use of drug products is governed, in general, by the requirements in part 312 (21 CFR part 312). Special provisions concerning radioactive drugs for certain research uses are contained in FDA regulations at 21 CFR 361.1. Under these special provisions, use of radioactive drug products in human subjects during the course of limited kinds of research projects may occur if the use is approved by a properly constituted Radioactive Drug Research Committee and if other conditions are met.

Section 502 of the act (21 U.S.C. 352) sets forth misbranding provisions applicable to drug products. Among other circumstances, a drug is considered misbranded if the product labeling is false or misleading or if the drug is dangerous to health when used as suggested in the labeling (21 U.S.C. 352(a) and (j)). For prescription drugs, section 502(n) of the act describes certain information that must be included in all advertisements or other printed materials. FDA's regulations also establish labeling and advertising requirements in more detail (21 CFR parts 201 and 202).

Section 510 of the act (21 U.S.C. 360) requires persons who own or operate establishments for the manufacture, preparation, propagation, compounding, or processing of drugs (with certain exceptions) to register the establishments with FDA. Individuals who must register their establishments under section 510 of the act must also file a list of all the drugs being made or processed at the establishment. Drug registration and listing regulations are codified at part 207 (21 CFR part 207).

II. Guidance: Regulation of PET Radiopharmaceuticals

FDA regulates PET radiopharmaceutical drug products used in purely physiologic research, where the results of such research are not used to guide patient management or

treatment decisions, as well as in investigational clinical trials and clinical practice. All facilities that manufacture PET radiopharmaceuticals must be registered with FDA in accordance with FDA regulations on the registration and listing of producers of drugs (part 207). Facilities that manufacture PET radiopharmaceuticals are not exempt from registration under § 1A207.10 because their activities do not fall within the scope of the regular course of the practice of the profession of pharmacy. This policy statement supersedes the “Nuclear Pharmacy Guideline; Criteria for Determining When to Register as a Drug Establishment” issued by FDA in May 1984.

A. Physiological Research

Facilities using PET radiopharmaceuticals for purely physiological research, where the results of such research are not used to guide patient management or treatment decisions, should establish a PET Regulatory Committee (PRC) in accordance with § 1A361.1 *Radioactive drugs for certain research uses* (21 CFR 361.1). The PRC will monitor all physiological research of the PET facility. Facilities using PET radiopharmaceuticals for purely physiological research are not required to submit an investigational new drug application (IND) or NDA as long as this research is intended to obtain basic information regarding metabolism or physiology and is not intended to guide or be part of therapeutic, diagnostic, or clinical management plans.

FDA will approve and monitor the PRC, which should consist of at least five individuals. In accordance with § 1A361.1(c), each PRC should include: (1) A physician recognized as a specialist in nuclear medicine; (2) a person qualified by training and experience to manufacture PET radiopharmaceuticals; and (3) a person with special competence in radiation safety and radiation dosimetry. The remaining PRC members should include individuals qualified in various disciplines pertaining to the field of nuclear medicine, and should be sufficiently diverse to permit expert review of the technical and scientific aspects of proposals submitted to the committee. In addition to the requirements in § 1A361.1(c) and with the exception of the member qualified by training and experience to manufacture PET radiopharmaceuticals, PRC membership should include a representative of a consumer group, and the members should not have scientific, clinical, financial, or administrative conflicts of interest.

The PRC should have three main responsibilities: (1) To approve research protocols; (2) to prepare annual reports; and (3) to determine when purely physiological research has ended.

In approving protocols, the PRC should: (1) Determine if the investigator meets the qualifications specified in the protocol; (2) review the research protocol design; (3) review and monitor the selection of research subjects; (4) ensure that the research subjects have signed informed consent documents; (5) review and monitor the quality of the PET radiopharmaceuticals administered; (6) evaluate all reports of adverse events; and (7) confirm concurrence of Institutional Review Board approval.

The annual report should follow the format and contents prescribed in § 1A361.1(c)(3), summarizing the conditions of use, doses, route of administration, protocols, adverse events reported in the safety information, and the chemistry, manufacturing, and control data. The PRC should submit the completed annual report to FDA.

The PRC is also responsible for determining when purely physiological research becomes investigational clinical use. This determination should be based on whether the

data obtained will be used in the diagnostic, therapeutic, or clinical management of patients. Once trials are proposed for investigational clinical use, the facility must submit an IND before starting to conduct the trials.

B. Investigational Use

Manufacturers of PET radiopharmaceuticals intended to be used in investigational clinical trials must submit an IND to FDA in accordance with the regulations in part 312. Institutions or investigators working together with the same PET radiopharmaceutical may submit one IND for that drug product, covering studies conducted at more than one site or institution.

C. NDA Approval

Submission of an NDA, in accordance with FDA regulations in part 314 (21 CFR part 314), is required for PET radiopharmaceuticals used in clinical practice. Institutions or investigators working together with the same PET radiopharmaceutical may submit one NDA for that drug product. All sites that produce the same drug product would be covered by the submitted NDA. Once an NDA is approved, other PET facilities with a radiopharmaceutical that is an equivalent finished product, but which did not participate in the NDA or did not submit manufacturing data, could submit an abbreviated new drug application (ANDA) demonstrating that their drug is bioequivalent to the innovator drug, in accordance with FDA regulations in part 314. Alternatively, the NDA holder could submit a supplement to add these other facilities as new manufacturing sites

PET radiopharmaceuticals are also subject to the adulteration and misbranding provisions of the act. Facilities where PET radiopharmaceuticals are manufactured are subject to inspection by FDA for compliance with CGMP requirements and other drug-related requirements.

Dated: February 17, 1995.
William B. Schultz,
Deputy Commissioner for Policy.

[FR Doc. 95-4691 Filed 2-24-95; 8:45 am]

BILLING CODE 4160-01-F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 210 and 211

[Docket No. 88N-0320]

Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs; Revision of Certain Labelling Controls; Partial Extension of Compliance Date

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule; partial extension of compliance date.

SUMMARY: The Food and Drug Administration (FDA) is announcing a continuation of the partial extension of the compliance date for a provision of the final rule, which was published in the Federal Register of August 3, 1993 (58 FR 41348). The document revised the current good manufacturing practice (CGMP) regulations for certain labeling control provisions. In the Federal Register of August 2, 1994 (59 FR 39255), FDA partially extended the compliance date for a provision of the regulation to August 3, 1995, and requested comments on the scope of this provision. The agency is further extending the compliance date to August 2, 1996. FDA is taking this action in order to adequately assess comments received on the scope of a particular provision of that rule.

DATES: The final rule published at 58 FR 41348, August 3, 1993, is effective August 3, 1994. The date for compliance with § 211.122(g) for items of labeling (other than immediate container labels) is extended to August 2, 1996. The date of compliance for all other provisions of the final rule remains August 3, 1994.

FOR FURTHER INFORMATION CONTACT:

Thomas C. Kuchenberg, Center for Drug Evaluation and Research (HFD-362).
Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301-594-1046. or

Paul J. Motise, Center for Drug Evaluation and Research (HFD-323), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301-594-1089.

SUPPLEMENTARY INFORMATION:

In the Federal Register of August 3, 1993 (58 FR 41348), FDA published a final rule that amended the CGMP regulations to require that certain special control procedures be instituted if cut labeling is used. One of these procedures requires the use of "appropriate electronic or electromechanical equipment to conduct a 100-percent examination for correct labeling during or after completion of finishing operations" (§ 211.122(g)(2)).

On May 4, 1994, FDA received a citizen petition from five trade associations requesting that the agency take a number of actions including, but not limited to, extending the August 3, 1994, effective date of this rule as it applies to labeling (other than the immediate container labels) as defined in section 201(m) of the Federal Food, Drug and Cosmetic Act (the act) (21 U.S.C. 321(m)). The petition stated that additional time was needed because of the unavailability of bar code or machine readers as well as other equipment necessary to orient the labeling codes properly, and requested that FDA reopen its administrative record to reassess the scope of a certain provision of the regulation, as discussed below in this document.

On May 6, 1994, the agency received an additional petition from a trade association that requested, among other things, a 1-year stay of the effective date; the petitioner stated that additional time was needed to locate, install, and validate scanning equipment and other necessary equipment to orient items properly for bar code scanning.

Appropriate electronic or electromechanical equipment primarily consists of systems that scan identity codes printed on labeling. If an incorrect code is detected, the defective labeling is ejected from the labeling line. FDA contacted vendors of this equipment and determined that while there was not a general shortage of system hardware, there was a possible shortage of contract engineering firms employed by some drug manufacturers to evaluate, select, purchase, install, qualify, and validate labeling verification systems.

In response to this situation, FDA extended the compliance date of § 211.122(g) as it applied to items of labeling (other than the immediate container label) to assess further the availability of equipment necessary for compliance with the final rule and to evaluate adequately other issues raised by petitioners.

The first petition also requested that the agency reopen the administrative record to receive additional comments on the application of § 211.122(g) to items of labeling (other than that of the immediate container label) as defined in section 201(m) of the act. Both citizen petitions contended that § 211.122(g) expanded the proposed scope of the provision from immediate container labels to all drug product labeling.

In response to the issues raised, FDA agreed to receive comments on this issue and to evaluate those comments in light of the existing language of § 211.122(g). The comment period ended on October 4, 1994, and since that time FDA has had a number of meetings with representatives of the labeling industry and others to determine control options available through current technology and to evaluate this information in light of comments received during the extended comment period.

In order to adequately assess this information, determine whether any possible revision of the regulation should result, and provide industry adequate time to fully comply with a final regulation, FDA is extending the compliance date of § 211.122(g) as it applies to items of labeling other than the immediate container label to August 2, 1996. Should FDA determine, after completing its assessment of the comments, that § 211.122(g) should be retained in its current state or revised, FDA will provide notice of that decision in a future issue of the **Federal Register**. The compliance date for the remainder of § 211.122, including § 211.122(g) as it applies to immediate container labels, was August 3, 1994. The agency emphasizes, however, that § 211.125 makes a waiver of labeling reconciliation conditional on a 100-percent examination for correct labeling performed in accordance with § 211.122(g)(2).

Dated: April 24, 1995.

William B. Schultz,

Deputy Commissioner for Policy.

[FR Doc. 95-10461 Filed 4-27-95; 8:45 am]

BILLING CODE 4160-01-F

Appendix C

Hearing Procedures When FDA Proposes the Imposition of Civil Money Penalties

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 5, 10, 17, and 20

[Docket No. 91N-0447]

RIN 0905-AD59

Civil Money Penalties: Biologics, Drugs, and Medical Devices

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing final regulations to establish hearing procedures for use when FDA proposes the imposition of administrative civil money penalties. This rule implements the civil money penalty provisions of several statutes: the National Childhood Vaccine Injury Act of 1986 (NCVIA), the Prescription Drug Marketing Act of 1988 (PDMA), the Safe Medical Devices Act of 1990 (SMDA), the Generic Drug Enforcement Act of 1992 (GDEA), and the Mammography Quality Standards Act of 1992 (MQSA).

EFFECTIVE DATE: August 28, 1995.

FOR FURTHER INFORMATION CONTACT: Joseph M. Sheehan, Center for Devices and Radiological Health (HFZ-84), Food and Drug Administration, 2098 Gaither Rd., Rockville MD 20850, 301-594-4765.

SUPPLEMENTARY INFORMATION:

I. Background

In the Federal Register of May 26, 1993 (58 FR 30680), FDA issued a notice of proposed rulemaking (NPRM) to establish procedures for hearings concerning the administrative imposition of civil money penalties by the agency. The NPRM noted that Congress had in recent years given FDA authority to impose civil money penalties in the NCVIA, the PDMA, the SMDA, and the GDEA. FDA requested that comments be filed by July 26, 1993.

Subsequently, a trade association requested an extension of time to file comments, and, in the Federal Register of July 27, 1993 (58 FR 40103), the agency extended the deadline for comments to August 25, 1993. In the July 27, 1993, Federal Register, FDA corrected an inadvertent error in the proposed rule and added a reference to civil money penalties authority provided for in the MQSA. The MQSA was added to the list of statutes covered by proposed part 17 insofar as the MQSA provided for the administrative imposition of civil money penalties.

Also, as an interim measure pending adoption of proposed part 17, FDA issued a regulation in the Federal Register of September 22, 1993 (58 FR 49190), under which it could temporarily conduct civil money penalties hearings pursuant to part 12 (21 CFR part 12). FDA is now revoking procedural regulations that it issued as a temporary measure pending adoption of part 17. This revocation will be effective when these part 17 regulations become effective. Specifically, § 5.99 (21 CFR 5.99) (as published at 58 FR 34212, June 24, 1993) and § 10.50(c)(21) (21 CFR 10.50(c)(21)) (as published at 58 FR 49190) were issued to allow FDA to use part 12 for civil money penalties proceedings on an interim basis. Because this delegation is no longer needed and because retention of these provisions in the Code of Federal Regulations would be confusing, FDA is revoking §§ 5.99 and 10.50(c)(21) when the new part 17 becomes effective.

As to any pending civil money penalty administrative actions that were subject to Notices of Opportunity for Hearing under part 12, when these part 17 regulations become effective, FDA will send letters to the respondents explaining that the agency intends to reinstitute the actions by the complaint and answer process of part 17. None of the pending actions has yet reached the point in the process of publication of a Notice of Hearing under 21 CFR 12.35. Since part 17 was specifically drafted to govern administrative hearings on civil money penalty assessments, its use for pending actions will not prejudice the respondents and will assure consistency in the adjudication of these matters. If, for any reason, there is a stay of the effectiveness of these part 17 regulations, the agency will proceed with the pending civil money penalty administrative actions under current 21 CFR 5.99, 10.50(c)(21), and part 12.

II. Summary of and Response to Comments

In response to FDA's NPRM, the agency received 12 public comments. Most came from device manufacturers or their representatives and device manufacturer trade associations. In addition, one consumer group and the administrative Conference of the United States commented. What follows is a summary of and response to each comment. Most of those commenting made more than one comment. Except for those comments that are not germane to a particular proposed section of part 17, the comments are considered in connection with the proposed sections to which they are related. In addition to the changes

discussed below, a number of editorial changes of the text of the final rule have been made to improve the clarity of the regulation.

A. General Comments on the Preamble

In responding to comments and formulating a final rule, FDA has balanced competing concerns: Namely, the interests of potential defendants in securing as many procedural safeguards as practicable, and the interests of the public in an efficient process that effectively implements the statutes. FDA is very conscious of the need to provide due process for companies and individuals from whom the Government is seeking civil money penalties, and the comments were carefully evaluated against this standard. At the same time, for the civil money penalty remedy to become an effective enforcement tool under the statute, the administrative process must be able to proceed with predictability and efficiency. The industry, as a whole, benefits from an efficient administrative civil penalties process in that such a system will help to maintain consistency in enforcement and thereby protect the majority of companies who stay in compliance against unfair competition from the small minority of firms that do not.

Accordingly, in developing this final rule, FDA has sought to establish an efficient, predictable system that processes cases in a fair and responsible manner, while affording defendants adequate procedural safeguards. As benchmarks, the agency has examined other existing civil money penalty processes, particularly as administered by the Environmental Protection Agency (EPA) and by the Inspector General of the Department of Health and Human Services (HHS). (See HHS regulation on Medicare Exclusions and Civil Money Penalties, 42 CFR part 1005; EPA Civil Penalties and Permit Revocation Regulation, 40 CFR part 22; Program Fraud Civil Remedies Regulation for HHS, 45 CFR part 79; and Program Fraud Civil Remedies Regulation for EPA, 40 CFR part 27).

These regulations provide a variety of procedural rights. FDA has selected from among these various provisions to create a fair hearing process. In response to comments, FDA has made over 25 changes in the final rule (see concluding section of this preamble), in addition to numerous clarifications throughout the preamble. For example, procedural safeguards under part 17 include motions for summary decisions, interlocutory appeal from rulings of the presiding officer, settlement conferences, allowing the parties to determine an appropriate settlement, and providing additional time before the hearing for the exchange of exhibits, witness lists, and written testimony. All of the EPA and HHS regulations provide for appeal of presiding officer's initial decision to an appeals board. EPA has an Environmental Appeals Board, while HHS has the Departmental Appeals Board (DAB). FDA has determined (see paragraph 101 below) that it would be an appropriate use of agency resources, as well as an efficient and effective means for handling appeals, to have the DAB serve as the reviewing authority for appeals of decisions by presiding officers on civil penalty actions.

The DAB is generally recognized as a fair and effective adjudicative forum. The DAB is an independent body within HHS with expertise in adjudication of civil money penalties. Accordingly, FDA will use that board, at least initially, for the adjudication of all appeals, including review of default judgments, interlocutory appeals, and appeals from initial decisions under this part. Elsewhere in this issue of the Federal Register, FDA is publishing a final rule in which the Commissioner of Food and Drugs delegates to the DAB the authority for the adjudication of appeals.

While a number of comments to the proposed rule sought procedures virtually identical to procedural rights available in civil litigation in Federal district courts, another comment urged that FDA use a more efficient complaint and answer procedure to streamline the process. These part 17 regulations provide a level of procedural safeguards consistent with that provided in other existing civil money penalties regulations. FDA believes that these procedures afford a respondent an impartial forum for the adjudication of any contested civil money penalty assessments.

1. Two comments questioned the use of administrative civil money penalties in connection with the PDMA and the NCVIA. Those commenting argued that, without specific congressional authority, FDA may not administratively impose civil money penalties, but must seek them through court proceedings. Additionally, another comment argued that FDA may not bind any future statutory grant of civil money penalties authority to part 17 hearing procedures.

FDA disagrees with the position that civil money penalties in connection with the PDMA and the NCVIA may not be imposed administratively, for the reasons stated in the preamble to the NPRM (58 FR 30680 through 30681). FDA acknowledges that the issue has not been directly addressed by the courts, but it agrees with the comment of the Administrative Conference of the United States that “any challenge to FDA’s authority to impose penalties administratively under such statutes (as the NCVIA) should be unsuccessful, *cf.*, *United States v. International Harvester*, 387 F. Supp. 1338 (D.D.C. 1974).”

As to implementation of any future civil money penalty statutory provision, FDA has reconsidered the desirability of determining in advance the use of part 17 procedures. Although the use of part 17 procedures to implement future civil money penalty legislation may be entirely appropriate, the agency prefers to preserve the flexibility to determine the procedures that will apply to specific statutory language once enacted. Section 17.1 has been modified to reflect this change.

2. One comment raised the concern that FDA has thus far not been delegated authority to impose civil money penalties by the Secretary of Health and Human Services (the Secretary). The comment’s premise is incorrect. The Secretary has delegated to the Commissioner of Food and Drugs (the Commissioner) all authority given the Secretary under the Federal Food, Drug, and Cosmetic Act (the act). (See § 5.10(a)(1).) (See also section 903 of the act (21 U.S.C. 393).) In addition, the Secretary has delegated to the Commissioner authority to perform all functions vested in the Secretary by Congress under section 351 of the Public Health Service Act (the PHS Act) (42 U.S.C. 262) concerning biologic recall orders. (See 5 CFR 5.10(a)(5).) The Secretary has granted the Commissioner authority to impose civil money penalties under the NCVIA. (See § 5.10(a)(35).) Also the Secretary delegated to the Commissioner authority granted the Secretary under the MQSA, which includes authority to impose civil money penalties. (See 21 CFR 5.10(a)(36).)

3. One comment requested FDA to correct its misquoting in the NPRM regarding the language of section 17(f) of the SMDA (21 U.S.C. 333(g)) by using “and” when the statute provided “or”.

The preamble to the NPRM stated (58 FR 30680 at 30681) that “civil money penalties are not authorized against persons who violate section 519(a) of the act (21 U.S.C. 360i(a)) * * * or section 520(f) of the act (21 U.S.C. 360j(f)) * * * unless the violation constitutes a significant *and* knowing departure from such requirements or a risk to the public health.” [emphasis added.] In the July 27, 1993, **Federal Register** (58 FR 40103

through 40104), FDA corrected its inadvertent misquote. Section 17(f) of the SMDA (21 U.S.C. 333(g)(1)(B)) states that civil money penalties shall not apply to any person who violates the requirements of section 519(a) or 520(f) “* * * unless such violation constitutes (I) a significant or knowing departure from such requirements, or (II) a risk to public health * * *.” [emphasis added]

Conversely, another comment argued that FDA had been inadvertently correct and that the legislative history shows that Congress had actually intended that the violations in question constitute significant *and* knowing departures in order to be punishable by civil money penalties. FDA rejects this argument because Congress’ intent is clear from the language of the statute. The legislative history contained in the Conference Report on the SMDA also supports FDA’s interpretation (H. Conf. Rept. 959, 101st Cong., 2d Sess. 29 (1990)).

4. Another comment stated that FDA should make clear that civil money penalties are in addition to other remedies available under law, not in lieu of them. FDA agrees that the agency has the authority to use civil money penalties in addition to other judicial and administrative remedies, if appropriate.

5. One comment asserted that violations of medical device reporting, current good manufacturing practice (CGMP), and tracking regulations should be enforced through civil money penalties. FDA agrees that these violations, as well as others, are suitable candidates for civil money penalty actions where authorized by the SMDA. FDA does not intend to rule out the use of civil money penalties in any situation provided for by law. Nor does FDA believe that civil money penalties need be the only remedy it may use to enforce these violations.

6. A comment urged the use of civil money penalties in lieu of warning letters for serious violations of law. FDA advises that its normal practice is to give prior notice by a warning letter or other means before taking more significant enforcement action. However, in the case of very serious violations or other special circumstances, the agency can and will continue to initiate judicial enforcement actions, as may be appropriate with or without the customary prior notice. Civil money penalties were not intended to take the place of warning letters; rather, civil money penalties were intended to assist the agency in safeguarding the regulatory system.

On April 21, 1995, President Clinton directed agencies to use discretion to modify penalties for small businesses. FDA’s traditional approach, by which the agency usually provides written warning to encourage voluntary correction of violations before undertaking the imposition of regulatory sanctions, is in keeping with the President’s directive. Also, as discussed in paragraph 25, in addition to establishing the respondent’s liability, FDA must prove the appropriateness of the penalty under the applicable statute in administrative civil money penalty actions.

7. One comment requested that the agency set forth specific examples of what will constitute substantial compliance with device tracking regulations such as assigning a percentage of trackable devices that would constitute “substantial compliance.” Until FDA has gathered more information on how and to what extent industry has complied with the device tracking regulations, it would be premature for the agency to present such specific, defining examples. FDA declines to do this at this time.

8. Yet another comment proposed that all civil money penalty proposals be cleared through the Department of Health and Human Services prior to implementation. Because

the Commissioner of Food and Drugs has been delegated authority to impose civil money penalties as noted in comment 2 of section II.A. of this document, the agency declines to adopt the comment's suggestion. However, as previously noted in the preamble and in paragraph 101 below, FDA has selected the DAB, at least initially, as the reviewing authority for appeals of civil penalty matters. Thus, the DAB's decision will constitute final agency action on contested FDA civil money penalties matters.

9. Several comments noted the absence of any prohibition against ex parte communications with the presiding officer. FDA agrees that restrictions on communications with the presiding officer concerning matters involved in part 17 hearings would be appropriate. Therefore, the agency has added § 17.20 to provide restrictions on ex parte communications.

10. Another comment requested that FDA specifically state that its part 17 regulation does not provide for a private right of action. FDA advises that only Congress can create a private right of action. FDA's regulations are not intended to create such a right.

11. One comment requested that FDA make explicit the authority of the parties and of the presiding officer to use alternative dispute resolution (ADR) in resolving a dispute under part 17. FDA agrees that settlement discussions should be encouraged. Therefore, the presiding officer has been given authority to require the parties to attend settlement conferences, which could include a conference held before an impartial third party, including the presiding officer, another administrative law judge, or a professional mediator. This change is reflected in revised § 17.19, and the agency believes it is a sufficient authorization for the use of ADR procedures.

12. The same comment suggested that FDA clarify whether an appeal to the Commissioner after an initial decision is required before a respondent may seek judicial review. The comment noted that in *Darby v. Cisneros*, 113 S.Ct. 2539 (1993), the Supreme Court determined that agency regulations that permit, but do not require, an aggrieved party to seek administrative review of a presiding officer's decision, allow parties to forego the option of administrative review and proceed directly to court. The comment stated a preference for requiring that a party seek administrative review of a presiding officer's decision before going to court, asserting that to be a sensible allocation of responsibilities between courts and agencies. FDA agrees and accepts the suggestion that FDA recast the regulation to ensure that a respondent must request administrative review, which is now made to the DAB, before seeking judicial review. Section 17.51(c) has been revised accordingly.

13. One comment criticized the proposal on grounds that the new part 17 will limit respondents' ability to reasonably contest the agency's allegations, but did not provide specifics to support the assertion. Absent any specific concerns raised by the comment, FDA can only reiterate that the agency believes these procedures reasonably accord due process and offer respondents a fair opportunity to contest the Center's allegations before an impartial presiding officer.

14. One comment took issue with that portion of the preamble of the NPRM which establishes FDA headquarters in Rockville, MD, as the "venue of choice for hearing procedures." The author of the comment urged that hearings take place in the FDA district office in whose jurisdiction the violations are alleged to have occurred. The author further argued that the burden of proof for change of venue from the districts where the alleged violations occurred should rest with the Center rather than the respondent. FDA believes this comment would be more persuasive if the presiding officer were an FDA official from

the pertinent district office. However, since the administrative law judge's principal office is in Rockville, MD, and other types of administrative hearings are held there (e.g., hearings under part 12 of FDA's procedural regulations), Rockville, MD, is the most logical and appropriate venue in most cases. FDA notes that the presiding officer has ample discretion to change the venue of the hearing when the Rockville location would present a significant hardship to the respondent.

15. Another comment recommended that FDA establish an internal procedure such as an intra-agency council of senior compliance officials and representatives from the Office of the Chief Counsel to assure the fair exercise of prosecutorial discretion in choosing which civil penalty cases to bring and how large a penalty to seek.

FDA agrees that it is important to exercise enforcement discretion in a fair and reasonable manner. Due to the newness of the civil penalties authority and the lack of FDA precedents in this area, the Office of Regulatory Affairs, Office of Enforcement, will establish coordinating procedures to help assure consistent policies in exercising civil money penalties authority agencywide. This will augment FDA's existing multilevel process that reviews all compliance actions proposed by the field and Centers, including civil money penalties, and which includes review by the Office of the Chief Counsel. If FDA determines that additional review procedures are appropriate after further experience assessing civil money penalties, it can establish those as a matter of internal agency procedure and not regulation.

B. Comments on Specific Sections

Section 17.3—Definitions

16. One comment noted that proposed § 17.3 defined several terms including “defective,” “knowing departure,” “significant departure,” and “minor violations,” used in the SMDA, but that the defined terms were not used elsewhere in the proposed rule and, therefore, were unnecessary. The comment urged that it should be made clear that the purpose of the definitions section is to define certain terms used in the SMDA, not terms used in 21 CFR part 17.

FDA agrees that the final rule should clarify that these defined terms apply to specific acts giving rise to civil money penalties, and has revised § 17.3 to reflect these changes. The agency has also modified the definition of “person” or “respondent” in § 17.3(b) to provide additional examples of potential respondents. Finally, FDA has included by reference in § 17.3 definitions from the act, Title 21, Code of Federal Regulations, and the PHS Act as they may be used in part 17 proceedings.

17. Another comment took issue with FDA's interpretation of the phrase “significant departure” as that term is used at 21 U.S.C. 333(g)(1)(B)(i), which applies to certain recordkeeping and reporting requirements for devices (21 U.S.C. 360i(a)) and to CGMP requirements for devices (21 U.S.C. 360j(f)). Proposed § 17.3(c), which is now § 17.3(a)(1), defined significant departure as a “departure from requirements which is neither isolated nor inconsequential.” The comment contended that this definition is likely to be met more often than not in the case of CGMP violations. The comment further argued that this result was contrary to the intent of Congress.

FDA notes that the comment cited no statutory language or legislative history regarding the definition of “significant departure,” although a review of the conference

report (H.R. Conf. Rep. No. 959, 101st Cong., 2d Sess. 29 (1990)) indicates that Congress did not limit a “significant departure” as the comment advocated. FDA believes, however, that the proposed definition could be improved to state that a significant departure includes a single major incident or a series of incidents that collectively are consequential. Section 17.3 has been amended to reflect this interpretation and to clarify that “significant departure” is being defined for the purposes of interpreting 21 U.S.C. 333(g)(1)(B)(i).

The agency emphasizes that it will not seek assessments of civil money penalties for trivial violations. FDA cannot list all violations that it regards as “inconsequential,” and believes that it can and will make reasonable judgments about the importance of violations.

18. One comment requested that the definition of “knowing departure” be revised. The author would have “knowing” limited to actual knowledge. FDA’s proposed definition stated that “knowing departure means actual knowledge of departure from requirements, or acting in deliberate ignorance of such departure, or acting in reckless disregard of such departure.” FDA disagrees with the comment. Part 17 defines “knowing” consistently with the definitions of “knowingly” or “knew” in the act as amended by the GDEA in 1992 (now 21 U.S.C. 321(bb)). Nothing in the SMDA or its legislative history suggests that the definition of “knowing” in 21 U.S.C. 333(g)(1)(B)(i) was intended to be more restrictive than the definitions of “knowingly” or “knew” that were added to the act by the GDEA in 1992. FDA has revised the definition of “knowing” to clarify that it is being defined for the purposes of interpreting 21 U.S.C. 333(g)(1)(B)(i).

19. Another comment maintained that the specific acts giving rise to civil money penalties are defined much too broadly. For example the author of the comment maintained that “minor violations” is too broadly defined. In proposed § 17.3, the term “minor violations” was defined as “violations which are isolated and inconsequential.”

The term “minor violations,” as used in 21 U.S.C 333(g)(1)(B)(ii), prohibits the assessment of civil money penalties for minor violations against a person who demonstrates substantial compliance with the requirements of 21 U.S.C. 360i(e) and (f), which relate to device tracking and correction reports. FDA believes that the term “minor violations” was used by Congress to prohibit the assessment of civil penalties when a departure from requirements does not rise to a level of single major incident or a series of incidents that are collectively consequential. FDA has revised the final rule (§ 17.3(a)(3)) accordingly and has clarified that “minor violations” is being defined for the purposes of interpreting 21 U.S.C. 333(g)(1)(B)(ii). FDA notes that this definition of “minor violation” is the converse of that adopted for significant departure as used in 21 U.S.C. 333(g)(1)(B).

20. FDA received several comments on the definition of “defective.” As proposed, § 17.3(a)(4) defined defective to include “any defect in performance, manufacture, construction, components, materials, specifications, design, installation, maintenance, service, or any defect in mechanical, physical and chemical properties in a device.” The comments expressed concern about possible broad implications of the proposed definition. In the final rule, FDA has generally retained the proposed definition but clarified that it is included in the defined terms solely for the purpose of interpreting 21 U.S.C. 333(g)(1)(B)(iii), which pertains to the very narrow area of devices that may be prepared, packed or held under insanitary conditions.

One comment argued that the inclusion of “performance” in the definition of “defective” is overly broad because it includes potential user error in the operation of the device. The comment suggested “performance” should be eliminated from the definition.

The intent of 21 U.S.C. 333(g)(1)(B)(iii) was to exempt, from potential assessment of civil penalties, those violations that may result from preparing, packing, or holding devices under insanitary conditions but that do not involve “defective” devices.

FDA agrees that performance failures based solely on user error unrelated to the conditions stated in 21 U.S.C. 351(a)(2)(A) or unrelated to problems with the device itself would not be considered a “defect in performance” of the device. The agency has revised the definition to make it clearer that “defect in performance” refers to “defect in performance of a device,” not to defect in performance of a user.

21. The same comment also recommended that the definition of “defective” in § 17.3 be amended to add the following statement: “Defective service and maintenance are included within the scope of this definition only to the extent that such defects are the result of negligence.”

FDA does not believe that a different standard should be applied to service and maintenance than to other activities covered by the definition, such as manufacture and construction. Therefore, the agency is not adopting the suggested amendment to the definition. FDA notes that it does not envision minor deviations from established maintenance or service schedules as being the basis for a civil money penalty action. FDA has clarified the definition of “defective” to substitute “or” for “and” in the phrase “any defect in the mechanical, physical, or chemical properties of a device,” since a defect in any one of these properties would cause the device to be “defective.”

22. Another comment requested that the definition of “defective” for purposes of civil money penalty actions incorporate the concept that a device is defective only if the device could reasonably be expected to pose a risk of some harm or not to function as intended because of the defect.

FDA disagrees. FDA will not seek civil money penalties because of trivial defects. However, defects are deviations that can affect the quality or performance characteristics of a device. To require a showing that the deviation is expected to cause harm or malfunction would shift the standard to allow more deviations and to provide less public health protection. The civil money penalty remedy is intended to promote the public health and the adopted definition of “defective” for purposes of 21 U.S.C. 333(g)(1)(B)(iii) supports this goal.

Section 17.5—Complaint

23. A comment remarked that § 17.5 does not contain any safeguards to ensure that FDA will only bring actions in those instances where it believes in good faith after properly conducting an investigation that violations have occurred sufficient to warrant civil money penalties. The comment did not identify what those safeguards should be. Although FDA declines to change § 17.5, as the answer to comment 15 makes clear, FDA’s review process for assessing civil money penalties should ensure that the agency will bring such actions only under the circumstances stated in the comment.

24. One comment argued that a complaint should specify “all facts” on which FDA is relying. FDA believes that the requirement regarding the contents of the complaint filed under part 17, as proposed, is consistent with other civil processes. For example, a complaint filed under Rule 8(a) of the “Federal Rules of Civil Procedure,” requires only “* * * (2) a short and plain statement of the claim showing that the pleader is entitled to relief * * *.” The requirements for a complaint are also consistent with the previously cited EPA and HHS Program Fraud Civil Remedies regulations.

FDA intends to file complaints that provide a reasonable description in sufficient detail for a respondent to have a fair understanding of the bases for the action. Moreover, the regulations requiring production of documents (§ 17.23) and exchanges of witness statements and exhibits (§ 17.25) provide for detailed presentations of factual information.

25. The same comment argued that the complaint should justify the amount of civil penalties being sought in accordance with factors identified in § 17.34. Again, FDA believes that a complaint filed under part 17 satisfies the requirements of notice pleading.

FDA recognizes that under the Administrative Procedure Act (APA) (5 U.S.C. 556(d)), as interpreted by the Supreme Court in *Director, OWCP v. Greenwich Collieries*, 114 S. Ct. 2251, 2257 (1994), the agency has the burden of proof on the respondent's liability and on the appropriateness of the penalty in light of the factors specified in the statute to be taken into account in determining the penalty. However, the proof that is required by the APA and specified in §17.33(b) is to be presented by the Center at the time of the hearing, not, as the comment suggests, in the complaint. In order to clarify that the burden of proof referenced in the APA requires the Center to prove the respondent's liability and the appropriateness of the penalty under the applicable statute, § 17.33(b) has been revised to state that "in order to prevail, the Center must prove respondent's liability and the appropriateness of the penalty under the applicable statute by a preponderance of the evidence."

26. This same comment called for "the intervention of [an] impartial, non-investigating party regarding whether an administrative complaint is sustainable." FDA believes that part 17 already provides for such an "impartial non-investigating party" in the form of a presiding officer, who is an administrative law judge qualified under 5 U.S.C. 3105.

27. Another comment objected that the regulation does not provide for a separation of investigatory and adjudicatory functions and stated that civil money penalty proceedings should be among those hearings to which separation of functions applies. FDA has added §17.20 to provide restrictions on ex parte communications with the presiding officer. Since the DAB will be adjudicating appeals in civil money penalties proceedings, there is no need to adopt separation-of-functions rules in these proceedings.

28. Yet another comment complained that §17.5(a) fails to identify anyone in FDA management who must approve the decision to impose a civil money penalty. Further, the author of the comment stated a belief that an initial determination of whether or not civil money penalties should be imposed should be made prior to the service of a complaint.

FDA advises that such an initial determination is in fact made. As described in paragraph 15, FDA has an established review procedure for enforcement cases, and that process will have added coordination for civil money penalties cases due to the newness of the authority and the lack of FDA precedents. However, since this is an institutional decision, it is not appropriate to designate a single individual as the agency's decisionmaker.

29. Yet another comment argued that notice pleading such as that provided for in § 17.5(b)(1) is inappropriate in light of the limited discovery provided for under these regulations. The comment called for either a more detailed notice in the complaint or greater discovery.

As discussed in paragraphs 24 and 61, FDA believes expanded discovery and plead-

ing are not necessary. FDA intends to file complaints that provide a reasonable description in sufficient detail for respondents to have a fair understanding of the bases for the action.

30. One comment requested that FDA first put a respondent on notice via a warning letter before it files a claim for civil money penalties. FDA advises that as with FDA's judicial enforcement remedies, it will normally give prior notice by a warning letter or other means, although there may be exceptional circumstances where no prior warning would be given.

Section 17.7—Service of Complaint

31. One comment stated that an affidavit as proof of service should suffice only when service is made by personal delivery. FDA agrees that an affidavit is most appropriate when service is made by personal delivery, and has amended §17.7(b)(1) to refer to "personal delivery."

32. A comment expressed concerns about the costs to be incurred by both the Center and the respondent as a result of these administrative procedures. FDA was mindful of the costs of litigation when it proposed part 17, and has sought to draft these procedures to minimize costs to all concerned. For example, providing for written direct testimony rather than oral direct testimony will significantly reduce the time and costs associated with hearings before the presiding officer.

Section 17.9—Answer

33. One comment argued that § 17.9 should provide for amendments to an answer after submission. FDA advises that it intends that complaints and answers may be amended on motion of the parties throughout the proceeding to conform to proof as justice may require. The "Federal Rules of Civil Procedure" follow this method for amendment of pleadings, allowing the motions to be ruled on by the district judge. Similarly, the presiding officer has been given this authority, which is so provided in the final rule (§17.9(d)).

34. A comment argued that 30 days is not sufficient to file an answer and that 60 days should be allowed for this purpose. FDA advises that if 30 days is not sufficient, a respondent may apply for more time upon a showing of good cause. (See §17.9(c).)

35. One comment observed that § 17.9(c) provides for a request for an extension of time within which to file an answer, which request is to be ruled on by the presiding officer, who at that stage will not have been appointed. Under proposed § 17.12, the presiding officer is appointed only after the respondent has answered. The comment requested that the final rule change the procedure.

FDA agrees and is changing the rules to eliminate § 17.12, which is unnecessarily repetitious, to include the definition of "presiding officer" in § 17.3, and to add a provision to § 17.5(d) for the assignment of the presiding officer upon the filing of the complaint.

36. Another comment objected that the proposed rules allow for the default of a respondent who fails to answer a complaint because extraordinary circumstances prevented it from responding within a particular timeframe.

FDA believes the regulation, as proposed, adequately addresses this point. Section 17.9(c) provides for an extension of time within which to file an answer when the respondent can show good cause. Additionally, a respondent may file a motion to reopen a default judgment on the grounds that extraordinary circumstances prevented the respondent from filing an answer. This should provide the relief that the comment requested.

Section 17.11—Default Upon Failure to File An Answer

37. A comment argued that § 17.11 should apply an “excusable neglect” standard, not an “extraordinary circumstances” test, for determining when relief from default for failure to answer should be granted. FDA prefers the “extraordinary circumstances” test, which, although somewhat harder to meet, is justified by the need to encourage respondents to respond in a timely fashion. Additionally, both EPA’s and HHS’s Program Fraud Civil Remedies regulations use an “extraordinary circumstances” test for determining whether to set aside a default judgment.

38. Another comment recommended that the language set forth in § 17.11(a) be modified to contain a requirement for the Commissioner to stay the initial decision of default upon a showing of extraordinary circumstances. FDA has changed § 17.11 regarding the issuance of a decision based upon default to allow the presiding officer to issue the initial decision rather than the Commissioner. The determination of whether to set aside a default judgment is an administrative matter that is better suited for initial review by the presiding officer, and which would be subject to appeal to the DAB.

39. The same comment stated that it is imperative that the term “extraordinary circumstances” be fully defined. FDA disagrees. To attempt to define and thus limit the circumstances which will be deemed “extraordinary” would be futile. FDA could not possibly anticipate all “extraordinary circumstances.” Indeed, such an attempt would probably not be in the interest of respondents as a group, since it would necessarily limit the kinds of circumstances that could be considered “extraordinary” and, therefore, in which a default decision could be set aside.

40. Yet another comment requested that no time limit be imposed on the remedy set forth in proposed § 17.11(c) concerning late filing of an answer. FDA disagrees. It is difficult to conceive of “extraordinary circumstances” that would justify extending the period for filing an answer or motion before the initial decision becomes final and binding. The regulation sets forth a reasonable procedure for the presiding officer to set aside a default judgment upon the showing of extraordinary circumstances by the respondent.

41. A comment requested that, in order for a default judgment to be entered for failure to answer a complaint, the Center should be required to prove that the complaint was received by the respondent. FDA agrees and has amended § 17.11 accordingly.

42. A comment advocated a provision authorizing a party to move to disqualify a presiding officer in order to assure a fair and impartial hearing. The agency advises that such a motion, carefully documented and based upon good cause, may be filed without a provision in these rules specifically authorizing it. The APA (5 U.S.C. 556(b)) authorizes disqualification of a presiding officer based on the filing in good faith of a timely and sufficient affidavit.

Section 17.13—Notice of Hearing

43. One comment argued that § 17.13 should contain clear standards, with reasonable timeframes, for setting the date, time, and place of the hearing or prehearing conference. Further, the comment suggested that the rules should clarify that the presiding officer sets all hearing dates.

FDA believes that it is currently clear that the presiding officer sets all hearing dates. However, FDA disagrees that the rules should set timeframes for a hearing or prehearing

conference. Scheduling depends on many variables, including the schedule of the presiding officer, the length of the hearing, the number of witnesses, etc. The presiding officer needs flexibility to schedule prehearing conferences, testimony, and briefing within the limits set forth in the regulation. Accordingly, additional specific time limitations are not being added to the regulations.

44. One comment requested that § 17.13 explicitly provide that either the notice of hearing or the complaint state specifically and in detail each violation alleged and the factual basis for it. The complaint is required to state the allegations of liability against the respondent, including the statutory basis for liability, to identify the violations that are the basis for the alleged liability, and to state the reasons that the respondent is responsible for the violations. In addition, the notice of hearing requires a statement as to the nature of the hearing and the legal authority and jurisdiction under which the hearing is to be held, as well as a description of the procedures for the conduct of the hearing.

FDA declines to make the requested change. The agency believes that the regulations, including § 17.5(b), require that a complaint provide a respondent with a reasonable description in sufficient detail for a respondent to have a fair understanding of the bases for the action and the issues for the hearing. FDA has clarified in § 17.13 that the notice of hearing is to be served on the respondent after the answer has been filed.

45. Another comment expressed the view that proposed § 17.13(f), which is now § 17.13(e), allows ex parte communications between the Center and the presiding officer without participation or comment by the respondent. The comment requested that ex parte communications not be permitted.

As noted in comment 9 above, § 17.20 has been added to restrict ex parte communications under part 17. However, FDA believes that ex parte contacts are necessary with respect to scheduling of the hearing or prehearing conference, and are contemplated for such administrative purposes. Ex parte scheduling contacts are common at agencies throughout the Federal Government and are not improper under § 17.20. All scheduling decisions made before the notice of hearing is served are subject to change on motion of the respondent, in any event.

Section 17.15—Parties to the Hearing

46. One comment argued that § 17.15 should specify that parties may settle issues prior to the hearing without admitting liability. FDA advises that there is no need to specifically state that the parties can stipulate that a settlement does not carry with it an admission of liability.

The regulation provides that the parties may agree to a settlement of all or a part of the matter. It would be inappropriate to limit by regulation the issues that may or may not be covered in a settlement agreement. The final rule allows for wide latitude in settlement agreements.

47. Another comment requested that FDA specifically state that respondent's counsel may be present and participate at the hearing. FDA agrees, and has amended the regulation to add § 17.15(c) accordingly.

48. A comment recommended that the final rule state whether a settlement pursuant to § 17.15(b) is to be incorporated in the initial decision or is instead to be an independent agreement between the parties. The comment went on to state that, if the settlement is to be incorporated in an independent agreement, the complaint should be dismissed.

FDA advises that a settlement agreement is to be an independent agreement. However, FDA believes that it is not necessary to require the dismissal of the complaint upon the filing of a settlement agreement, as the case will be considered resolved and closed by the filing of the settlement agreement, and the agreement will so provide.

Section 17.17—Summary Decisions

49. A comment objected to the inclusion of a summary decision procedure in proposed part 17. FDA affirms the desirability of summary decision procedures in this context. In many situations, the facts will be undisputed and the only question to be decided is one of law. In such cases, time and money can be saved through a summary decision procedure.

50. The author of the same comment urged that, if summary decision procedures are retained, time to respond to a motion for summary decision should be 30 days, not 10. FDA agrees that 10 days is a short time in which to respond. Therefore, FDA is extending from 10 to 30 days the period in which to respond to a motion for summary decision.

51. Another comment argued that summary judgment for the Center should never be granted without the filing of an affidavit prior to the motion being filed. The comment asserts that failure to require an initial affidavit prior to a motion for summary decision denies the respondent the opportunity to verify the facts set forth in the complainant's pleadings.

The language in § 17.17 setting forth the use of affidavits in filing for a motion for summary decision is virtually identical to the language in Rule 56 of the "Federal Rules of Civil Procedure." Respondent may oppose the motion for summary decision with specific facts or opposing affidavits. The presiding officer may only grant the motion if the pleadings, affidavits, and other material in the record show that there is no genuine issue as to any material fact. Additionally, the presiding officer may direct further evidentiary proceedings on facts still at issue. Accordingly, FDA believes the rule provides adequate safeguards for the due process rights of the respondent.

52. Another comment asked the following: (1) Whether or not a proceeding will be stayed pending an interlocutory appeal granting partial summary decision, and (2) whether judicial review of such a decision is a prerequisite to interlocutory relief.

The decision to stay a proceeding pending appeal is within the discretion of the presiding officer, who will make such a decision based on the facts before him or her at the time. Similarly, FDA believes that in some circumstances it would not be necessary or appropriate to have an interlocutory appeal of a presiding officer's partial summary judgment decision on civil money penalties. A decision by a district court granting partial summary judgment is usually not reviewable by the court of appeals on an interlocutory basis. (See, e.g., *King v. California Co.*, 224 F.2d 193 (5th Cir.), *cert. denied*, 352 U.S. 1007 (1955); *Marino v. Nevitt*, 311 F.2d 406 (3rd Cir. 1963); *Acha v. Blame*, 570 F.2d 57 (2nd Cir. 1978).)

53. Another comment suggested that respondents should be given an opportunity to conduct discovery before FDA may bring a motion for summary decision. FDA advises that the presiding officer has the discretion to deny the motion, grant the motion, or order a continuance to permit affidavits or additional evidence to be obtained under § 17.23(a).

54. Another comment argued that a party should have the option of taking an inter-

locutory appeal on a partial summary decision order or appealing the issue after a final disposition of the entire matter. FDA believes that a party should be permitted to request interlocutory appeal and has amended § 17.17 and added § 17.18 accordingly.

Economy of effort dictates that partial summary decisions not be appealed routinely to the entity designated by the Commissioner to decide appeals (currently the DAB) on an interlocutory basis, but FDA has agreed to provide the option to permit interlocutory appeal within the discretion of the presiding officer and the entity hearing the appeal. In general, appeal of all issues after a final disposition of the entire matter would reduce unnecessary review time for resolution of civil money penalty cases.

55. One comment expressed a concern about language in the preamble of the proposed rule to the effect that the SMDA permits FDA to bypass the administrative hearing procedure and pursue the imposition of civil money penalties in Federal court. FDA has reconsidered the language stated in the NPRM.

The statute authorizes assessment of civil money penalties in an administrative procedure under the SMDA (21 U.S.C. 333(g)(2)), and this is the most efficient manner of imposing civil money penalties. Judicial review would only occur in the United States Court of Appeals as initiated by the respondent (21 U.S.C. 333(g)(3)).

Section 17.19—Authority of the Presiding Officer

56. A comment objected that § 17.19 does not set forth criteria upon which the presiding officer is to base the assignment of a hearing date. This hearing date, according to the comment, should be within at least 30 days of the giving of written notice in all hearings.

FDA does not believe it is necessary to set forth such criteria. The presiding officer will set dates based upon factors such as his or her own schedule, the length of the hearing, and the number of witnesses. FDA hopes that hearings will be completed expeditiously, but a 30-day period from notice until actual hearing may not be enough time in complex hearings.

57. A comment complained that proposed § 17.19(b)(14), which is now paragraph (b)(15), does not define “related or similar proceedings.” FDA chose not to define this phrase because of the difficulty of anticipating all proceedings that might be “related or similar.” The comment provides no help in defining the phrase, and the agency does not believe that a definition is necessary.

58. A comment argued that FDA should not have the power to subpoena documents because this would impermissibly broaden FDA’s enforcement powers. FDA disagrees. Congress has specifically provided that FDA may subpoena documents under certain circumstances in civil money penalty proceedings. (See 21 U.S.C. 333(g)(2)(A) and 21 U.S.C. 335(b)(1)(A)). This statutory authority is similar to that granted to, and exercised by, other Federal entities, such as the EPA and the HHS Inspector General, and the agency expects to use this authority to the extent provided by law. (See paragraph 60 below.)

59. Yet another comment complained that proposed § 17.19(b)(16), which is now paragraph (b)(17), which permits the presiding officer to “waive, suspend, or modify any rule,” gives too much discretion to the presiding officer. The comment urged that this language be deleted. FDA disagrees. Under 21 CFR 12.70(m), the presiding officer in formal FDA evidentiary hearings has had this authority for many years, and there have been few, if any, allegations that this authority has been abused.

60. One comment opposed the authorization in § 17.19(b)(5) for issuance of subpoenas by the presiding officer in proceedings under section 303(g)(2)(A) of the act (21 U.S.C. 333(g)(2)(A)). The author of the comment stated that this section of the SMDA authorizes only an investigative subpoena, not a hearing subpoena.

FDA disagrees with the comment's interpretation of the SMDA, which, in pertinent part, reads as follows: "In the course of any investigation, the Secretary may issue subpoenas requiring the attendance and testimony of witnesses and the production of evidence that relates to matters under investigation." FDA interprets this to allow the agency to issue subpoenas related to a civil money penalty proceeding at any time, including during the adjudication of the penalty. The legislative history indicates that the agency was given authority to subpoena records and witnesses relevant to the civil penalty proceeding. In addition, the statutory phrase "attendance and testimony of witnesses and the production of evidence" reflects an intention that the testimony and documents be useable at the hearing itself.

Section 17.23—Discovery

61. A comment stated that FDA should authorize depositions, written interrogatories, and requests for admissions. The comment argued that, while brevity and economy are worthwhile goals, respondents need fuller discovery. The comment asserts that discovery depositions are necessary tools in the formation of a response to a civil money penalties complaint. Specifically, the comment objects to the presentation of hearing testimony orally without the opportunity to depose witnesses before the hearing.

FDA disagrees, and does not believe that additional forms of discovery are necessary for due process to be accorded to respondents. EPA and HHS adjudicative procedures provide these discovery mechanisms under their regulations enacted pursuant to the Program Fraud Civil Remedies Act (31 U.S.C. 3801, *et. seq.*). However, 31 U.S.C. 3803(g)(3)(B)(ii) requires that discovery be authorized to the extent allowed by the presiding officer. The program statutes that these part 17 provisions implement do not require that discovery be provided and FDA is not required to provide for discovery under the APA, which governs these procedures. (See *Pacific Gas and Electric Co. v. F.E.R.C.*, 746 F.2d 1383, 1387 (9th Cir. 1984); *McClelland v. Andrus*, 606 F.2d 1278, 1285 (D.C. Cir. 1979).)

FDA has discretion to determine the extent of discovery to which a party is entitled in an administrative hearing. In order to allow the parties to present a witness' testimony in the event that a witness would be unavailable for the hearing, FDA has added § 17.23(e) to provide for depositions in limited circumstances. Specifically, the presiding officer may order depositions upon a showing that the information sought is not available by alternative methods and there is a substantial reason to believe that relevant and probative evidence may not otherwise be preserved for presentation by a witness at the hearing.

In order to provide advance notice of each witness' testimony prior to cross-examination at the hearing, FDA has changed § 17.37(b) to require that direct testimony of witnesses be submitted in written form. Section 17.25(a) requires that parties exchange written testimony at least 30 days before the hearing. This should eliminate any concern that a party may be unfairly surprised by a witness' testimony presented at a hearing. Section 17.19(b)(10) has also been changed to authorize the presiding officer to recall a witness for additional testimony upon a showing of good cause. The failure of a party to

provide written direct testimony of a witness before a hearing will result in exclusion of the witness' testimony.

The prehearing production of documents and exchange of exhibits by both parties, coupled with the right to cross-examine witnesses at the hearing and recall witnesses upon a showing of good cause, obviates the need for routine depositions, written interrogatories, and requests for admission. Recent changes to the "Federal Rules of Civil Procedure" have significantly reduced the number of depositions available to parties in Federal court litigation because of their expensive and time consuming nature (Fed. R. Civ. Proc. 30(a)(2)). FDA believes that its provision for written direct testimony is more cost effective for all concerned. Additionally, to ensure timely exchange of documents between the parties, § 17.23(a) has been changed to require that requests for production of documents be answered 30 days after the request, and that the request be made no later than 60 days before the hearing, unless otherwise ordered by the presiding officer.

62. Another comment argued that § 17.23 should specifically authorize the presiding officer to grant protective orders for trade secrets and confidential commercial information.

FDA agrees and has added a new paragraph to § 17.19(b)(18) to the final rule authorizing the presiding officer to issue protective orders for the protection of trade secrets and confidential commercial information. In order to reflect this change and to eliminate any confusion that resulted from the proposed rule, FDA has revised §§ 17.28, 17.33, and 17.41 to more clearly state the disclosure rules related to part 17 hearings. Additionally, in § 17.23(d)(3) FDA has added that the burden of showing that a protective order is necessary is on the party seeking the order.

63. A comment argued that § 17.23 should specifically exempt "privileged" information from access by FDA, even under a protective order. The comment expressed concern that the subsection authorizing the presiding officer to grant a protective order does not address trade secrets and confidential commercial information.

The agency believes that it would not be appropriate for FDA to be denied access to such information. FDA typically has broad access to confidential documents through its regulatory activities and carefully safeguards the confidentiality of those documents. As discussed in comment 62, the presiding officer is authorized to issue a protective order that will prevent public disclosure of such information.

Section 17.25—Exchange of Witness Lists, Witness Statements, and Exhibits

64. A comment took issue with the harshness of the "extraordinary circumstances" test for relief for failure to exchange witness lists, statements, and exhibits. The author argued that this relief should be granted only when a party did not substantially comply or noncompliance was in bad faith.

FDA disagrees with the comment's interpretation of proposed § 17.25(b)(2). However, the agency has clarified that § 17.25(b)(2) and (b)(3) refer to the timely exchange of witness lists under § 17.25(a). The exclusion of other evidence not exchanged in accordance with § 17.25(a) is within the discretion of the presiding officer as noted in § 17.25(b)(1). The agency believes that it is fair and appropriate to grant relief from sanctions for failure to follow the requirements for the timely exchange of witness lists only if there are "extraordinary circumstances."

To provide additional time for the parties to prepare for the hearing, FDA has changed the deadline for the exchange of witness lists, exhibits, and prior written state-

ments of witnesses from 15 days to 30 days before the hearing. Section 17.25(c) has also been changed to add that objections to authenticity of documents, exchanged pursuant to § 17.25(a), must be made no later than 5 days before the hearing, or the documents will be deemed authentic.

Section 17.27—Hearing Subpoenas

65. A comment argued that the authority of the presiding officer under § 17.27 to subpoena witnesses broadens FDA's power and is not authorized under the PDMA and the NCVIA. FDA agrees that because neither the PDMA nor the NCVIA grants FDA subpoena powers, § 17.27 should not be made applicable to hearings under these statutes.

FDA is altering § 17.27 to clarify that subpoenas may only be issued by the presiding officer to the extent authorized by law. In order to ensure that a party can prove that a witness has been served with a subpoena, FDA has deleted the provision on service of subpoenas by first-class mail. Revised § 17.27(e) provides that subpoenas shall be served in the manner prescribed for service of a complaint in § 17.7.

Section 17.30—Computation of Time

66. Another comment contended that the “less than 7 days” time period stated in proposed § 17.30(b) should be changed to be “less than 11 days” if the summary decision response time in § 17.17 remains at 10 days. The comment explained that Rule 6(a) of the “Federal Rules of Civil Procedure” uses the “less than 11 days” rule specifically to avoid routine requests for extension of the 10-day time for responding to most motions, a period that may include only 5 business days. FDA is changing the summary decision response time to 30 days (see paragraph 50), which should obviate the need for routine requests for extension of the time for responding to motions for summary decision.

Section 17.33—The Hearing and Burden of Proof

67. A comment urged that the presiding officer be required to exclude from the public portion of a hearing all evidence involving what he or she has determined to be trade secrets or confidential commercial information. FDA believes that this is unnecessary.

The agency has revised § 17.33(d) to clarify the scope of information that may be presented in a closed hearing. Under § 17.33 the presiding officer will apply existing laws and regulations to protect trade secrets and confidential commercial information from public disclosure.

68. Yet another comment urged that the Center be required to prove its case by “clear and convincing evidence” in light of what the comment refers to as the extremely broad definitions of punishable acts in § 17.3, rather than by a “preponderance of evidence” as provided for in the proposal.

FDA believes that the definitions in § 17.3 as revised provide adequate explanation of the defined terms. The acts for which civil money penalties may be assessed, however, are delineated in the various statutory schemes for civil penalties to which part 17 applies. The “preponderance of evidence” test is common in many civil proceedings, and is the appropriate standard of proof to be applied by the presiding officer under 5 U.S.C. 556(d). (See *Sea Island Broadcasting of S.C. v. Federal Communications Commission*, 627 F.2d 240 (D.C.Cir.), *reh. den.*, *cert. denied*, 449 U.S. 834 (1980).) FDA rejects the comment.

Section 17.34—Determining the Amount of Penalties and Assessments

69. Two comments urged that FDA include “degree of culpability” as a factor in determining the amount of a civil money penalty under § 17.34. The degree of culpability is listed as a factor to be considered in 21 U.S.C. 333(g)(2)(B). Because the statutory civil money penalty provisions implemented by this regulation differ, FDA has referenced the statutory scheme under which the penalty is assessed for purposes of determining the amount of penalty, rather than listing factors in § 17.34. Accordingly, FDA rejects the comment.

70. Another comment argued that FDA should factor in the degree to which a respondent has cooperated with FDA. FDA believes that the presiding officer could properly consider the extent of cooperation under the authority provided in § 17.34(c).

Section 17.35—Sanctions

71. Another comment argued that the sanctions section (§ 17.35) is unclear, unnecessarily harsh, and goes beyond the authority delegated to FDA. The comment urged FDA to describe the types of misconduct to which the section applies and to limit sanctions. Such sanction provisions are not novel. For example, they are included in regulations used by EPA and HHS to implement statutory civil money penalty provisions and are designed to enable the presiding officer to manage proceedings effectively. FDA cannot anticipate all types of misbehavior and misconduct that could give rise to sanctions. Further, FDA cannot anticipate what sanctions may be appropriate for particular conduct in a particular situation. The presiding officer must have discretion in this area, and § 17.35 is consistent with the discretion that may be delegated to the presiding officer under the APA (5 U.S.C. 556(c)). FDA therefore declines to accept the comment.

72. A comment argued that FDA needs to provide a means of appeal of an order of the presiding officer imposing sanctions. FDA agrees. Sanctions should be subject to requests for interlocutory appeal. Section 17.18 has been added to allow for interlocutory appeal of matters certified by the presiding officer to need immediate review. However, the rule does not contain a provision for the automatic stay of proceedings before the presiding officer pending appeal.

73. A comment argued that the sanctions listed in § 17.35 are too harsh and that financial penalties might be more appropriate than the loss of the right to defend against or prosecute a civil money penalty claim.

FDA disagrees. The sanctions imposed in § 17.35 are similar to sanctions available under Rule 37 of the “Federal Rules of Civil Procedure,” as well as under the Program Fraud Civil Remedies regulations of EPA and HHS, and are a justifiable means of compelling the parties to adhere to the orders and rulings of the presiding officer. As in a proceeding before a judge in Federal court, a party’s recalcitrance in disobeying a presiding officer’s order in an administrative hearing should not be tolerated. The wide range of sanctions listed in § 17.35 provide flexibility for the presiding officer who might be presented with a party’s failure to comply with an order through refusal or neglect.

74. In connection with appellate rights, one comment urged that the parties be afforded the right of judicial review of sanctions imposed during a part 17 hearing.

FDA advises that it has no authority to provide for an appeal to the courts before the agency’s final decision is issued. Under § 17.51, the final decision constitutes final

agency action which is subject to judicial review. The entire record that forms the basis of the final decision would be available to the reviewing Court of Appeals.

75. Another comment disagreed with proposed § 17.35(g), which provides that the presiding officer may order a party to pay expenses. This remedy, the author argued, is unenforceable and outside the authority of the Government to provide.

FDA does not agree that it lacks the authority or that such an order of the presiding officer is unenforceable. However, because of the wide range of other sanctions available to the presiding officer for regulating the conduct of the hearing, FDA has made the change requested by the comment and eliminated § 17.35(g) as proposed.

Section 17.37—Witnesses

76. One comment took issue with what was viewed as a requirement that a cross-examining party pay a witness' travel expenses in a situation where direct testimony was submitted in writing. This was not FDA's intention in drafting § 17.37. FDA advises that it intends that a party submitting a witness' testimony in writing is responsible for paying the travel and other expenses of that witness on cross-examination at the hearing. FDA has added § 17.37(g) to clarify its intention.

77. A comment objected to § 17.37 because it could be interpreted to permit rebuttal witnesses and evidence to be submitted without any provision for discovery or identification, as provided for in connection with a party's presentation of its case in chief. FDA advises that, because rebuttal testimony and other rebuttal evidence are limited in scope and in quantity, requirements for notice and discovery are not necessary. Thus, FDA is not specifically providing for discovery or notice of a rebuttal witness' appearance. However, § 17.39(g) allows the presiding officer to permit the parties to introduce rebuttal witnesses and evidence. Implicit in this authority is the authority to set the terms of rebuttal testimony, as justice may require.

78. Yet another comment argued that § 17.37(e) is unduly broad in permitting cross-examination of witnesses on matters other than those within the scope of his or her direct examination. The comment recommended that the rules for cross-examination be predicated upon the "Federal Rules of Evidence."

FDA disagrees. In the interest of truth seeking in general and in the interest of procedural economy, FDA prefers § 17.37(e) as proposed. This provision is similar to what EPA and HHS provide in their Program Fraud Civil Remedies of regulations, which give the presiding officer discretion to allow cross-examination of witnesses beyond the scope of their direct examination, rather than limiting cross-examination to only those matters within the scope of direct examination. Otherwise, the opposing party would have to request that a subpoena be issued to a witness by the presiding officer, making the witness its own in a manner that unnecessarily wastes time.

Section 17.39—Evidence

79. One comment objected to § 17.39 to the extent that it renders privileged information nondiscoverable. Section 17.39 is similar to Rule 45 of the "Federal Rules of Civil Procedure," which allows privileged information to be withheld by a person responding to a subpoena. FDA rejects the comment.

80. Another comment objected to language in § 17.39(b), which allows the presiding officer discretion to apply the "Federal Rules of Evidence." According to the com-

ment, the presiding officer is given authority to invoke the “Federal Rules of Evidence” in an arbitrary and capricious fashion, which, the comment alleges, abridges the due process rights of both parties. The comment does not, however, provide any details to support its assertion.

FDA disagrees with the comment. To the contrary, under § 17.39(b) presiding officer is allowed to apply the “Federal Rules of Evidence” *when appropriate* which is similar to what EPA and HHS provide in their Program Fraud Civil Remedies regulations. Section 17.39(f) has been changed to substitute the relevant language of Rule 408 of the “Federal Rules of Evidence” in place of the reference to Rule 408 in the proposed rule.

Section 17.41—The Administrative Record

81. A comment suggested that § 17.41 should include an explicit exemption to the “open record” provision, not subject to the discretion of the presiding officer, if the officer has determined that a portion of the record contains trade secrets or confidential commercial information.

FDA believes this to be a good suggestion, and has so provided. Trade secrets, confidential commercial information, information the disclosure of which would constitute a clearly unwarranted invasion of personal privacy, or other information that would be withheld from public disclosure under 21 CFR part 20 are to be protected from disclosure by order of the presiding officer. Additionally, FDA is amending 21 CFR 20.86, concerning disclosure of information in administrative proceedings, to include part 17.

82. Another comment was concerned that the proposal does not contain a provision authorizing the correction of the hearing transcript and recommended that a provision similar to that contained in 21 CFR 12.98(d) be included in § 17.41. FDA has made the requested change in § 17.41(a).

Section 17.43—Posthearing Briefs

83. A comment objected to the requirement that briefs be filed simultaneously and be limited to 30 pages. According to the comment, these restrictions may prejudice respondents, however, the comment does not state how respondents may be prejudiced.

Under § 17.43, a party may file a longer brief if the presiding officer has found that the issues in the proceeding are so complex or the administrative record is so voluminous as to justify longer briefs. In the absence of a showing that simultaneous briefs will prejudice a party unfairly, FDA sees no reason to change this requirement. Additionally, parties may file proposed findings of fact and conclusions of law. FDA has added to § 17.43 that proposed findings of fact and conclusions of law are also limited to 30 pages unless the presiding officer orders otherwise.

84. Another comment requested that § 17.43 be clarified to state whether the 30-page limitation includes exhibits and attachments. FDA advises that the 30-page limitation does not include exhibits and attachments unless some material is made part of an exhibit or attachment to avoid the 30-page limitation when the material should reasonably have been included in the main portion of the brief itself.

Section 17.45—Initial Decision

85. One comment complained that requiring the presiding officer to decide the case within 90 days will inherently increase the risk of an incorrect result, thereby allegedly

denying due process. FDA disagrees. Ninety days should be an ample amount of time for a presiding officer to decide most part 17 hearings. If the presiding officer needs more time, he or she may request that the entity deciding the appeal set a new deadline under § 17.45(c). As stated in the preamble, the DAB will be deciding, at least initially, appeals to the Commissioner for presiding officer decisions under this part, including a presiding officer's request for extending deadlines.

86. Another comment urged FDA to include timeframes for extensions of deadlines for rendering an initial decision. This would assure a speedier process, according to the comment. FDA disagrees. It is difficult if not impossible to set forth in a regulation the criteria for extending timeframes in issuing hearing decisions. FDA believes that attempting to do so would be unworkable.

87. Yet another comment urged that the initial decision be required to include a discussion of the reasons for the findings and conclusions upon which the decision is based. However, § 17.45 already requires that the initial decision shall contain findings of fact, conclusions of law, and the amount of any penalties imposed. Section 17.45(b) further elaborates on this requirement. In FDA's view, the regulation as proposed does not permit a "conclusory" initial decision as the comment seems to presuppose. FDA declines to make the requested change.

88. One comment requested that § 17.45 provide that the initial decision be automatically stayed pending disposition of an appeal or motion for reconsideration. FDA disagrees. The agency does not believe that such a provision is necessary since no civil money penalty can be imposed until there has been final agency action. The initial decision would not become final agency action until any appeal has been acted on, the appeal time has expired, or the respondent has stated an intention not to seek an appeal.

89. Another comment recommended that the word "may" (in § 17.45(c)), as it applies to the Commissioner's authority to set a new timeframe for issuing the initial decision, be changed to "shall." This, the comment alleges, would preclude indefinite delay in the issuance of an initial decision. FDA declines to adopt this comment. As indicated under comment 86, FDA believes it would be unworkable to specify all the criteria for determining when timeframes for issuing initial decisions may be extended. FDA reaffirms its intention that all such decisions be made promptly.

Section 17.47—Appeals

90. A comment suggested that § 17.47 should be modified to explicitly provide for an automatic stay of a decision pending an appeal or motion for reconsideration. As stated in a prior response (see paragraph 88 above), such an automatic stay is not necessary.

91. A comment requested that FDA make clear that the Commissioner's decision, which has been delegated to the DAB, not to consider an appeal or the affirmation of the presiding officer's decision on appeal constitutes final agency action subject to judicial review. FDA agrees with the comment and affirms that such events do constitute final agency action. However, the agency sees no reason to amend any regulation to accomplish this. This statement in the preamble should suffice.

92. A comment urged that oral argument of an appeal to the entity designated by the Commissioner to decide appeals (currently the DAB) be allowed. FDA disagrees. Oral argument would not provide the DAB with any additional information that could not be

included in the briefs allowed to be filed by the parties under § 17.47. The time required to conduct oral argument does not justify any advantage that might be gained from it.

93. A comment urged that FDA allow 60 days for submission of an appellate brief, especially considering the complexity of likely issues. The comment cites the part 12 practice of allowing 60 days for an appellate brief. FDA disagrees with the comment. The agency believes that issues raised in part 17 hearings will generally be less complex and the volume of testimony smaller than is the case concerning part 12 hearings. Thus, 30 days should be sufficient. If not, § 17.47 provides for extensions upon a showing of good cause.

94. A comment alleged that proposed § 17.47(f), which has been redesignated as § 17.47(g), favors appellees (which it alleges will usually be the Center) by allowing the appellee to make any argument based on the record in support of the initial decision or decision granting summary decision. This, the comment alleges, is unfair because the appellant does not have as much leeway.

FDA disagrees. The appellant has the discretion to determine the specific exceptions to the initial decision that are to be urged on appeal. Section 17.47(c) has been changed to clarify that in the notice of appeal the appellant must identify and support specific exceptions with citations to the record and explain the basis for the exceptions. Since the appellant may urge whatever exceptions it finds appropriate, FDA sees no prejudice in allowing the appellee to make arguments on matters contained in the record. If the entity deciding the appeal (currently the DAB) reverses on issues that the presiding officer considered pivotal, it may still affirm on other grounds if the appellee has raised such other grounds below. There should be no prejudice to either side as both sides have the record before them and can brief on appeal all issues raised in it. As explained in paragraph 95 below, FDA is amending § 17.47(h) to allow the DAB to request additional briefing when an issue has not been adequately briefed by the appellant.

95. Similar objection was raised to § 17.47(g), relating to the appellee's right to make any argument based on the record. The comment stated that if the purpose of this provision is to allow the appellee to anticipate sua sponte decisions by the Commissioner favorable to the appellant, the regulation would be better if recast as allowing the Commissioner to request both parties to address issues not raised by the appellant but determined to be important by the Commissioner.

As previously discussed the Commissioner has initially designated the DAB to conduct appeals of civil money penalty proceedings under this part. FDA advises that the purpose of the provision in § 17.47(g) is to allow the DAB or other entity deciding the appeal to affirm a decision based on issues raised before the presiding officer but that did not serve as a basis for the presiding officer's decision. This will allow the entity deciding the appeal to overrule the presiding officer on an issue considered pivotal by the presiding officer, but nevertheless to decide the matter in favor of the appellee on other issues based on evidence adduced at the hearing. However, FDA agrees with the comment that the entity deciding the appeal may wish to decide an issue that is not fully briefed by both parties. Therefore, FDA is amending § 17.47(h) to allow that entity discretion to request additional briefing if it: (a) Proposes to affirm an initial decision based on arguments not fully briefed by appellant, and (b) believes that additional briefing is necessary.

96. One comment took issue with the review standard of "substantial evidence on the whole record" in § 17.47. The comment argued that the standard of substantial evi-

dence on the whole record is applicable for appellate court review of agency action, but should not be applied by an agency head when the agency does not preside at the evidentiary hearing under the APA, 5 U.S.C. 557(b). The comment went on to state that the burden of proof by a preponderance of the evidence rests upon the complainant under 5 U.S.C. 556(d).

FDA agrees that the appropriate burden of proof before the presiding officer is a preponderance of the evidence, as explained in paragraph 68 above. However, the agency may limit review of the initial decision by the presiding officer if the powers of review have been limited by rule. See 5 U.S.C. 557(b).

FDA has provided that an administrative law judge serve as the fact finder in its civil money penalty actions. As the fact finder, the presiding officer is required to make his or her findings based on the preponderance of the evidence standard.

When an appeal is made to the DAB under part 17, the DAB, if it decides to review the initial decision, will review disputed issues of fact based on the standard of whether the initial decision is supported by substantial evidence on the whole record. Additionally, the final regulation in § 17.47 has set the standard of review on a disputed issue of law to be whether the initial decision is erroneous. These standards of review are similar to the HHS regulation on appeals of Medicare exclusions, 42 CFR part 1005. The purpose of limiting the scope of the DAB's review of appeals from the presiding officer is to allow the presiding officer to serve as the fact finder and to limit the DAB's reviewing powers to be similar to that of an appellate court. The APA permits the standards of review set forth in § 17.47 for the DAB's review of initial and summary decisions by the presiding officer.

97. Another comment suggested that only the respondent should be permitted to appeal an adverse initial decision. The comment supports its argument by noting that FDA's proposed procedures did not follow the EPA model, which precludes appeals by any party other than the defendant. However, as the comment points out, the EPA provision tracks the statute, 31 U.S.C. 3803(i)(2)(A)(i), with procedures that are statutorily imposed on EPA.

In enacting the civil money penalty provisions in the statutes to which this regulation applies, Congress did not choose to prescribe, other than in a general manner, the administrative procedures to be followed in FDA's assessment of civil money penalties. FDA therefore does not believe the Center should be precluded from requesting the DAB to review an initial decision with which the Center disagrees.

The comment questioned the fairness of allowing the Center to appeal an initial decision in favor of the respondent. Because FDA has revised the appeals provisions in the final rule to designate the DAB, at least initially, to make the decision for the Commissioner, the independent review by the DAB should eliminate speculation of possible bias of the reviewing authority. FDA notes that in civil cases where the United States is a party plaintiff, district court decisions that are adverse to the plaintiff may be subject to appeal by the plaintiff.

For example, the act (21 U.S.C. 360pp(a)) provides that Federal district courts shall have jurisdiction over civil penalties arising from prohibited acts (21 U.S.C. 360oo) pertaining to the regulation of electronic products. If the United States disagrees with a district court judgment as to the amount or lack of penalty, the Federal Rules of Appellate Procedure (Rule 4) authorize an appeal. Under part 17, the Center's right to appeal an initial

decision to the DAB is consistent with appellate review authorized for civil cases in Federal district courts.

In cases that are appealed to the DAB, the DAB will normally issue a decision within 60 days. In circumstances where that is not practicable, the DAB will notify the parties of the anticipated time period for ruling on the appeal. Accordingly, § 17.47(j) has been changed to add “if practicable” to the 60-day timeframe for the DAB’s decision.

98. A comment requested that the time to file an appeal be set at 60 days and that the time to submit a brief be set by the presiding officer. FDA disagrees. The only reason given by the author of the comment for this extension of time is that the issues involved are likely to be more factually and legally complex than those in the typical civil penalty adjudications by other agencies. Further, the comment suggested that a change in the deadlines would avoid routine requests for extension of time.

The agency believes that it is far from clear that the issues involved in part 17 hearings will be more factually and legally complex than those in “typical civil penalty adjudication.” However, in order to alleviate the concerns expressed by the comment, FDA changed § 17.47(b)(2) to provide that the 30-day time limit to file the notice of appeal may be extended by the Commissioner or the entity designated by the Commissioner to hear appeals (currently the DAB), within his or her discretion, upon request of the appealing party for good cause shown. In order to ensure that a party has adequate time to respond to the brief filed in support of the appeal, § 17.47(d) has also been changed to allow the entity deciding appeals, within his or her discretion, to extend the time limit for the filing of a brief in opposition to the appeal upon request of the party and a showing of good cause.

99. Another comment recommended that § 17.47(d) not prohibit an appellant’s reply brief. The comment stated that, on a practical level, motions for leave to reply will regularly be filed typically accompanied by a brief. Further, the comment argues that, based on past practice, such briefs will be routinely read and considered in any case. FDA agrees and is amending § 17.47 to allow for a short (no more than 10 pages) reply brief.

100. One comment requested that FDA explain more clearly what FDA means in proposed § 17.47(i), which is § 17.47(j) in the final rule, for the Commissioner to “decline to review the case.” Indeed, FDA agrees, as the comment presupposes, a decision to decline to review the case has the same legal effect as a decision to affirm the initial decision summarily without further comment. Such a summary decision may be issued without findings of fact or conclusions of law.

In § 17.47(j), FDA has added that a decision by the DAB to decline to review the case shall be the final decision, rendering the initial decision final and binding on the parties 30 days after the declination. For clarification of the possible actions by the entity designated by the Commissioner to decide the appeal, currently the DAB, FDA has changed § 17.47(j) in the final rule to authorize the entity to reverse the initial decision or decision granting summary decision. The proposed § 17.47(i) only provided that the Commissioner could reverse the penalty, but did not explicitly state that the initial decision could be reversed.

101. Another comment opposed any form of summary affirmance of a decision appealed by the Center. The author of the comment alleged that a respondent is entitled to an explanation, however concise, of the reasons why the Commissioner agrees with the presiding officer. According to the comment, the right to omit such an explanation

invites cursory review and inappropriately relieves the Commissioner of the burden of responsibility that accompanies the authority to penalize a manufacturer.

FDA rejects the comment and, in so doing, notes that summary affirmances are routinely used by the courts of appeals. Additionally, the EPA and HHS regulations on program fraud that were previously cited provide for similar affirmance of an initial decision by the presiding officer, as does the HHS regulation on Medicare exclusions and civil penalties. FDA continues to believe that a summary disposition is appropriate in various circumstances, such as where issues are not complex and where the evidence heavily favors the appellee.

Underlying the comment may be the concern that the Commissioner might be biased in favor of the Center, when deciding an appeal and using summary affirmances to do so. In order to provide the parties with an independent review of civil penalty appeals, eliminate speculation of possible bias by the reviewing authority, and to allow for more efficient and effective use of the Commissioner's resources, FDA has elected to designate the DAB to decide appeals under this part, at least initially.

The DAB serves as the reviewing authority for HHS administrative hearings in the previously cited regulations, as does the Environmental Appeals Board for EPA. These Boards have the training and resources to review appeals of civil penalty actions, whereas the Commissioner would be required to set up a separate process for handling civil penalty appeals. The DAB is the logical choice, at least initially, to review appeals of decisions rendered by the presiding officer in part 17 matters, while efficiently and effectively using agency resources.

FDA will use the DAB to decide appeals under part 17 for at least a 4-year period. After 4 years, FDA will evaluate the DAB's role and the Commissioner will determine whether to maintain or alter the delegation to the DAB.

Section 17.49—Delegated Functions

102. A comment suggested that § 17.49 should contain criteria for selecting and delegating authority to an individual under that section. Because FDA is initially providing that the DAB be designated as the entity to decide any appeals under this part, § 17.49 has been eliminated.

103. A comment alleged that § 17.49 allows the Commissioner to assign an agency party with an interest in the litigation to make the final decision on appeal, as long as the individual was not assigned to advise the Center. As noted in paragraph 101, appeals will initially be handled by the DAB. Therefore, any concern about an agency party's influence on the final decision should be eliminated.

104. A comment argued that all civil money penalty assessments should be finally decided by the Commissioner without delegation to another FDA official. As noted in the preceding paragraphs, FDA has provided, at least initially, for appeals to the DAB for a variety of reasons. Therefore, FDA rejects the comments.

Section 17.51—Judicial Review

105. A comment urged that FDA should not be allowed to seek judicial review of an adverse decision. Only a respondent should be allowed to do so, according to the comment. FDA agrees. Section 17.51 should not be interpreted to provide for the Center to seek judicial review. Once a final decision is rendered denying civil money penalties, this be-

comes the decision of the agency from which there is no judicial appeal by FDA or any of its Centers. Section 17.51 is being amended to clarify this issue.

III. Summary of Changes

1. In § 17.1, concerning the scope of the regulation, the reference to future statutory civil money penalty authority has been deleted. (See comment paragraph 1.)

2. In § 17.3(a), (b), (d), (e), and (f), references to definitions in the applicable statutes and regulations have been added. In § 17.3(a) the definition of “significant departure” has been changed to either a single major incident, or a series of incidents that are collectively consequential (paragraph 17). In section 17.3(a) the definition of “minor violations” has been changed to “departures from requirements that do not rise to a level of a single major incident or a series of incidents that are collectively consequential” (paragraph 19). Section 17.3(a)(4) has been revised to clarify that “* * * defect in performance * * *” refers to “* * * defect in performance, * * * or service of a device,” (paragraph 20). In § 17.3(b) scientific or academic establishment or governmental agency or organizational unit has been added to the definition of “person or respondent” (paragraph 16). In § 17.3(c) the definition of “presiding officer” has been added (paragraph 35). In § 17.3(g) the definition of Departmental Appeals Board has been added (paragraph 101).

3. Section 17.5(c) has been revised to provide for the right of the Center to amend its complaint (paragraph 33). Section 17.5(d) has been revised to provide that the presiding officer is assigned to the case upon filing of the complaint (paragraph 35).

4. Section 17.9(a) is revised to add that the respondents may answer without requesting a hearing. Section 17.9(b) is revised to add that allegations not denied are deemed to be admitted, and that all defenses must be stated in the answer (paragraph 33). Section 17.9(d) was added to provide that respondents may amend their answers (paragraph 33).

5. Section 17.11(a) is revised to add a requirement for proof of service and the authority of the presiding officer to enter default judgments and hold hearings on motions to reopen default judgments (paragraph 38). In § 17.11(a) the reference to the Commissioner has been deleted (paragraph 38).

6. Section 17.12 has been eliminated because the presiding officer is now appointed when the complaint is filed (paragraph 35).

7. Section 17.13 was changed to clarify that the notice of hearing is to be served on a respondent after an answer has been filed (paragraph 44).

8. Section 17.15(b) was revised to add a provision that settlement agreements are to be filed in the docket and do not require ratification by the presiding officer (paragraph 48). Section 17.15(c) was added to clarify that parties may be represented by counsel at the hearing (paragraph 47).

9. In § 17.17(a) the response time to motions for summary judgment has been extended from 10 days to 30 days (paragraph 50). Section 17.17(b) was changed to clarify that summary decision shall be granted when there is no genuine issue as to any material fact (paragraph 51). Section 17.17(e) now limits the ability of a party to obtain interlocutory review of a partial summary decision and refers to the DAB as, currently, the reviewing authority (paragraph 52).

10. New § 17.18 was added to provide for interlocutory appeal from a ruling of the presiding officer (paragraph 54).

11. Section 17.19(b)(3) was changed to authorize the presiding officer to require

parties to attend conferences for settlement (paragraph 11). A new § 17.19(b)(10) was added to authorize the presiding officer to allow a witness to be recalled for additional testimony (paragraph 61). Proposed § 17.19(b)(10) through (b)(17) have been renumbered. For consistency of language, in § 17.19(b)(13) (proposed § 17.19(b)(12)) summary “judgment” now reads summary “decision” when there is no “genuine” issue of material fact. A new § 17.19(b)(18) has been added to authorize the presiding officer to issue protective orders (paragraph 62).

12. New § 17.20, has been added to provide restrictions on ex parte communications (paragraph 9).

13. Section 17.21(c)(8) now includes discussion of “scheduling dates for completion of discovery” as an authorized use of a prehearing conference (paragraph 61). Section 17.21(d) has been changed to require the presiding officer to issue an order after a prehearing conference (paragraph 61).

14. In § 17.23(a) a requirement has been added that requests for “production, inspection, and copying” of documents be made no later than 60 days before the date of the hearing, unless otherwise ordered by the presiding officer.

The party served with the request must respond no later than 30 days after the request has been made (paragraph 61). In § 17.23(c) a reference to new § 17.23(e) has been added. A new § 17.23(d)(3) now places the burden of showing that a protective order is necessary on the party seeking the order (paragraph 62). Proposed § 17.23(d)(3) has been renumbered (d)(4). Section 17.23(e) has been added to provide for oral depositions under limited circumstances (paragraph 61).

15. Section 17.25(a) has been revised to change the deadline for the exchange of witness lists, prior written statements, and exhibits from 15 days to 30 days before the hearing (paragraph 64). For clarification, § 17.25(b)(2) and (b)(3) have been changed to specifically clarify that the paragraphs concern the admission of testimony by any witness whose name does not appear on the witness lists exchanged under § 17.25(a). Section 17.25(c) now imposes a deadline of “5 days” prior to the hearing for objection to authenticity of documents (paragraph 64).

16. Section 17.27(a) now explicitly limits the issuance of subpoenas to when such issuance is “authorized by law” (paragraph 65). For ease of proving service, § 17.27(e) has been changed to delete the provision on service of subpoenas by first class mail (paragraph 65).

17. Section 17.28(b) was revised to clarify that a protective order may be issued to protect information that would be withheld from public disclosure under the agency’s public information regulations in 21 CFR part 20 (paragraph 63).

18. For clarification, § 17.31(b) was changed to provide that an opposing party must be served with a copy of a document no later than when the document is filed in the docket. Section 17.32(a) now requires that the presiding officer also be served with a copy of documents filed with the Dockets Management Branch.

19. For clarification, in § 17.33(b) and (c) “is to” was replaced with “must”.

Section 17.33(b) has been clarified to add that the Center has the burden of proof to establish that the proposed penalty is appropriate under the applicable statute (paragraph 25). Section 17.33(d) was revised to include a reference to information that would be withheld from public disclosure under 21 CFR part 20.

20. Section 17.34 has been changed to refer to the statute under which the penalty

is assessed for purposes of determining the amount of the penalty. The DAB has been referenced as the entity currently designated by the Commissioner to decide appeals under this part in § 17.34(a) and (c) (paragraph 101).

21. Proposed § 17.35(g), which authorized the presiding officer to order the payment of costs as a sanction, has been deleted (paragraph 75). New § 17.35(g) now provides for interlocutory appeal to the entity designated by the Commissioner to decide appeals (currently the DAB) of sanctions imposed by the presiding officer (paragraph 72).

22. Section 17.37(b) now requires, rather than permits, that direct testimony of witnesses be submitted by written declaration under penalty of perjury. The proposed provision in § 17.37(b) on “sufficient time for other parties to subpoena witness” has been deleted in light of the addition of new § 17.37(g) (paragraph 76). For clarity, § 17.37(f)(2) was modified to explain more clearly that an officer or employee of a party who is “designated to be the party’s sole representative for purposes of the hearing” may not be excluded from hearing the testimony of other witnesses. Section 17.37(f)(3) has also been revised to make clear that each party may also have an individual, such as an expert witness, present at the hearing who would not be excluded from hearing other witnesses’ testimony. New § 17.37(g) was added to clarify that a cross-examining party need not subpoena the witness, and to require that a sponsoring party produce a witness at its own expense (paragraph 76).

23. In § 17.39(f), a modified version of the language of Rule 408 of the “Federal Rules of Evidence” has been substituted for the proposed reference to Rule 408 (paragraph 80). For clarification, in § 17.39(g) a reference to the discretion of the presiding officer was added.

24. In § 17.41(a) a provision has been added to allow for corrections for transcription errors (paragraph 82). Section 17.41(b) has been changed to reference the DAB as the entity currently designated by the Commissioner to decide appeals under this part. Section 17.41(c) has been revised to clarify that upon motion of any party the presiding officer shall protect from disclosure documents that would be withheld from public disclosure under the agency’s public information regulations at 21 CFR part 20 (paragraph 81).

25. Section 17.43 has been revised to add a page limit provision for filing of proposed findings of fact and conclusions of law (paragraph 83).

26. Section 17.45(c) has been changed to reference “the Commissioner or the entity deciding the appeal.”

27. Section 17.47 has been changed to authorize appeals to the DAB instead of to the Commissioner (paragraph 101). Section 17.47(b)(2) now provides that the Commissioner or other entity designated by the Commissioner to hear appeals (currently the DAB) has discretion to extend the 30-day time limit to file an appeal upon request of a party and a showing of good cause.

Section 17.47(c) has been revised to add a page limitation for briefs in support of appeals and a requirement that exceptions listed in the notice of appeal be explicitly supported by citations to the record (paragraph 94). The prohibition on the filing of an appellant’s reply brief in proposed § 17.47(d) has been deleted. Section 17.47(d) has been changed to allow the Commissioner or the entity designated by the Commissioner to hear appeals, currently the DAB, to extend the 30-day time limit for the filing of a brief opposing the appeal upon request of the party and a showing of good cause. New § 17.47(e) has been added to provide the right of an appellant to file a reply brief within 10 days of

being served with the appellee's brief (paragraph 99). Section 17.47(h) has been renumbered as § 17.47(k) and has been revised to add that the standard of review on a disputed issue of law is whether the initial decision is erroneous (paragraph 101). Proposed § 17.47(e) through (i) have been renumbered. New § 17.47(h) has been added to authorize the entity deciding the appeal (currently the DAB) to request additional briefing by the parties (paragraph 95). Section 17.47(j) has added "if practicable" to the 60-day deadline for the decision on appeal. For consistency of language, "summary judgment" was changed to "summary decision" in § 17.47(j), which was proposed § 17.47(i). In § 17.47(j) explicit language authorizing the entity deciding the appeal (currently the DAB) to reverse the initial decision or decision granting summary decision has been added (paragraph 100). Section 17.47(j) now clarifies that a decision by the entity deciding the appeal (currently the DAB) to decline to review the case shall be the final action of the agency and the initial decision shall be final and binding on the parties 30 days after the declination.

28. Section 17.48 has been changed to reference the DAB as the entity currently designated by the Commissioner to decide appeals under this part.

29. Section 17.49 has been deleted.

30. Section 17.51(a) now states that only a respondent may petition for judicial review or file a petition for stay of a decision by the Commissioner (paragraph 105). New § 17.51(c) makes explicit that exhaustion of an appeal to the entity deciding the appeal (currently the DAB) is a jurisdictional prerequisite to judicial review (paragraph 12).

31. Section 17.54 has been revised to state amounts assessed under part 17 are to be delivered to the Director of FDA's Division of Financial Management and then deposited in the U.S. Treasury.

32. In addition, the following revisions have been made to other regulations:

a. Section 5.99, regarding issuance of notices and orders relating to civil money penalties, has been deleted (see the Background section of this document).

b. Section 10.50(c)(21), regarding opportunities for a hearing under 21 CFR part 12, has been deleted (paragraph 9).

c. Section 20.86, regarding disclosure of data and information in administrative proceedings, has been revised to include part 17 (paragraph 81).

IV. Environmental Impact

The agency has determined under 21 CFR 25.24(a)(8) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

V. Analysis of Impacts

FDA has examined the impacts of the final rule under Executive Order 12866 and the Regulatory Flexibility Act (Pub. L. 96-354). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The agency believes that this final rule is consistent with the regulatory philosophy and principles identified in the Executive Order. In addition, the final rule is

not a significant regulatory action as defined by the Executive Order and so is not subject to review under the Executive Order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. The final rule specifies the procedures to be followed by persons who have the right to a hearing on the administrative imposition of civil money penalties by the agency. As such the rule does not impose any burden on regulated industry. Because the procedures themselves are protections and do not impose significant costs beyond what the underlying statute imposes, the agency certifies that the final rule will not have a significant economic impact on a substantial number of small entities. Therefore, under the Regulatory Flexibility Act, no further analysis is required.

List of Subjects

21 CFR Part 5

Authority delegations (Government agencies), Imports, organization and functions (Government agencies).

21 CFR Part 10

Administrative practice and procedure, News media.

21 CFR Part 17

Administrative practice and procedure, Animal drugs, Biologics, Civil money penalties hearings, Drugs, Generic drugs, Prescription drugs samples, Medical devices.

21 CFR Part 20

Confidential business information, Courts, Freedom of information, Government employees.

Therefore, under the Federal Food, Drug and Cosmetic Act and the Public Health Service Act and under authority delegated to the Commissioner of Food and Drugs, Title 21, Chapter 1 of the Code of Federal Regulations is amended as follows:

PART 5—DELEGATIONS OF AUTHORITY AND ORGANIZATION

1. The authority citation for 21 CFR part 5 continues to read as follows:

Authority; 5 U.S.C. 504, 552, App. 2; 7 U.S.C. 138a, 2271; 15 U.S.C. 638, 1261–1282, 3701–3711a; secs. 2–12 of the Fair Packaging and Labeling Act (15 U.S.C. 1451–1461); 21 U.S.C. 41–50, 61–63, 141–149, 467f, 679(b), 801–886, 1031–1309; secs. 201–903 of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 321–394); 35 U.S.C. 156; secs. 301, 302, 303, 307, 310, 311, 351, 352, 354, 361, 362, 1701–1706, 2101, 2125, 2127, 2128 of the Public Health Service Act (42 U.S.C. 241, 242, 242a, 242l, 242n, 243, 262, 263, 263b, 264, 265, 300u–300u–5, 300aa–1, 300aa–25, 300aa–27, 300aa–28); 42 U.S.C. 1395y, 3246b, 4332, 4831(a), 10007–10008; E.O. 11490, 11921, and 12591; secs. 312, 313, 314 of the National Childhood Vaccine Injury Act of 1986, Pub. L. 99–660 (42 U.S.C. 300aa–1 note).

§ 5.99 [Removed]

2. Section 5.99 *Issuance of notices and orders relating to the administrative imposition of civil money penalties under various statutes* is removed.

PART 10—ADMINISTRATIVE PRACTICES AND PROCEDURES

3. The authority citation for 21 CFR part 10 continues to read as follows:

Authority: Secs. 201–903 of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 321–394); 21 U.S.C. 41–50, 141–149, 467f, 679, 821, 1034; secs. 2, 351, 354, 361 of the Public Health Service Act (42 U.S.C. 201, 262, 263b, 264); secs. 2–12 of the Fair Packaging and Labeling Act (15 U.S.C. 1451–1461); 5 U.S.C. 551–558, 701–721; 28 U.S.C. 2112.

§ 10.50 [Amended]

4. Section 10.50 *Promulgation of regulations and orders after an opportunity for a formal evidentiary public hearing* is amended by removing paragraph (c)(21).

5. New part 17 is added to read as follows:

PART 17—CIVIL MONEY PENALTIES HEARINGS

Sec.

17.1 Scope.

17.3 Definitions.

17.5 Complaint.

17.7 Service of complaint.

17.9 Answer.

17.11 Default upon failure to file an answer.

17.13 Notice of hearing.

17.15 Parties to the hearing.

17.17 Summary decisions.

17.18 Interlocutory appeal from ruling of presiding officer.

17.19 Authority of the presiding officer.

17.20 Ex parte contacts.

17.21 Prehearing conferences.

17.23 Discovery.

17.25 Exchange of witness lists, witness statements, and exhibits.

17.27 Hearing subpoenas.

17.28 Protective order.

17.29 Fees.

17.30 Computation of time.

17.31 Form, filing, and service of papers.

17.32 Motions.

17.33 The hearing and burden of proof.

17.34 Determining the amount of penalties and assessments.

17.35 Sanctions.

17.37 Witnesses.

17.39 Evidence.

17.41 The administrative record.

17.43 Posthearing briefs.

17.45 Initial decision.

17.47 Appeals.

17.48 Harmless error.

17.51 Judicial review.

17.54 Deposit in the Treasury of the United States.

Authority: Secs. 301, 303, 307, 501, 502, 505, 510, 513, 516, 519, 520, 701 of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 331, 333, 337, 351, 352, 355, 360, 360c, 360f, 360i, 360j, 371); sec. 351, 354, 2128 of the Public Health Service Act (42 U.S.C. 262, 263b, 300aa-28); 5 U.S.C. 554, 555, 556, 557.

§ 17.1 Scope.

This part sets forth practices and procedures for hearings concerning the administrative imposition of civil money penalties by FDA. Listed below are the statutory provisions that as of August 28, 1995, authorize civil money penalties that are governed by these procedures.

(a) Section 303 (b)(2) through (b)(4) of the Federal Food, Drug and Cosmetic Act (the act) authorizing civil money penalties for certain violations of the act that relate to prescription drug marketing practices.

(b) Section 303(g) of the act authorizing civil money penalties for certain violations of the act that relate to medical devices.

(c) Section 307 of the act authorizing civil money penalties for certain actions in connection with an abbreviated new drug application or certain actions in connection with a person or individual debarred under section 306 of the act.

(d) Section 351(d)(2)(B) of the Public Health Service Act (the PHS Act) authorizing civil money penalties for violations of biologic recall orders.

(e) Section 354(h)(2) of the PHS Act, as amended by the Mammography Quality Standards Act of 1992, authorizing civil money penalties for failure to obtain a certificate, failure to comply with established standards, among other things.

(f) Section 2128 of the PHS Act authorizing civil money penalties for intentionally destroying, altering, falsifying, or concealing any record or report required to be prepared, maintained, or submitted by vaccine manufacturers pursuant to that section of the PHS Act.

§ 17.3 Definitions.

The following definitions are applicable in this part:

(a) For specific acts giving rise to civil money penalty actions brought under 21 U.S.C. 333(g)(1):

(1) *Significant departure*, for the purpose of interpreting 21 U.S.C. 333(g)(1)(B)(i), means a departure from requirements that is either a single major incident or a series of incidents that collectively are consequential.

(2) *Knowing departure*, for the purposes of interpreting 21 U.S.C. 333(g)(1)(B)(i), means a departure from a requirement taken: (a) With actual knowledge that the action is such a departure, or (b) in deliberate ignorance of a requirement, or (c) in reckless disregard of a requirement.

(3) *Minor violations*, for the purposes of interpreting 21 U.S.C. 333(g)(1)(B)(ii), means departures from requirements that do not rise to a level of a single major incident or a series of incidents that are collectively consequential.

(4) *Defective*, for the purposes of interpreting 21 U.S.C. 333(g)(1)(B)(iii), includes any defect in performance, manufacture, construction, components, materials, specifications, design, installation, maintenance, or service of a device, or any defect in mechanical, physical, or chemical properties of a device.

(b) *Person or respondent* includes an individual, partnership, corporation, association, scientific or academic establishment, government agency or organizational unit thereof, or other legal entity, or as may be defined in the act or regulation pertinent to the civil penalty action being brought.

(c) *Presiding officer* means an administrative law judge qualified under 5 U.S.C. 3105.

(d) Any term that is defined in the act has the same definition for civil money penalty actions that may be brought under that act.

(e) Any term that is defined in Title 21 of the Code of Federal Regulations has the same definition for civil money penalty actions that may arise from the application of the regulation(s).

(f) Any term that is defined in the PHS Act has the same definition for civil money penalty actions that may be brought under that act.

(g) *Departmental Appeals Board (DAB)* means the Departmental Appeals Board of the Department of Health and Human Services.

§ 17.5 Complaint.

(a) The Center with principal jurisdiction over the matter involved shall begin all administrative civil money penalty actions by serving on the respondent(s) a complaint signed by the Office of the Chief Counsel attorney for the Center and by filing a copy of the complaint with the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857.

(b) The complaint shall state:

(1) The allegations of liability against the respondent, including the statutory basis for liability, the identification of violations that are the basis for the alleged liability, and the reasons that the respondent is responsible for the violations;

(2) The amount of penalties and assessments that the Center is seeking;

(3) Instructions for filing an answer to request a hearing, including a specific statement of the respondent's right to request a hearing by filing an answer and to retain counsel to represent the respondent; and

(4) That failure to file an answer within 30 days of service of the complaint will result in the imposition of the proposed amount of penalties and assessments, as provided in § 17.11.

(c) The Center may, on motion, subsequently amend its complaint to conform with the evidence adduced during the administrative process, as justice may require.

(d) The presiding officer will be assigned to the case upon the filing of the complaint under this part.

§ 17.7 Service of complaint.

(a) Service of a complaint may be made by:

(1) Certified or registered mail or similar mail delivery service with a return receipt record reflecting receipt; or

(2) Delivery in person to:

(i) An individual respondent; or

(ii) An officer or managing or general agent in the case of a corporation or unincorporated business.

(b) Proof of service, stating the name and address of the person on whom the complaint was served, and the manner and date of service, may be made by:

(1) Affidavit or declaration under penalty of perjury of the individual serving the complaint by personal delivery;

(2) A United States Postal Service or similar mail delivery service return receipt record reflecting receipt; or

(3) Written acknowledgment of receipt by the respondent or by the respondent's counsel or authorized representative or agent.

§ 17.9 Answer.

(a) The respondent may request a hearing by filing an answer with the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857, within 30 days of service of the complaint. Unless stated otherwise, an answer shall be deemed to be a request for hearing.

(b) In the answer, the respondent;

(1) Shall admit or deny each of the allegations of liability made in the complaint; allegations not specifically denied in an answer are deemed admitted;

(2) Shall state all defenses on which the respondent intends to rely;

(3) Shall state all reasons why the respondent contends that the penalties and assessments should be less than the requested amount; and

(4) Shall state the name, address, and telephone number of the respondent's counsel, if any.

(c) If the respondent is unable to file an answer meeting the requirements of paragraph (b) of this section within the time provided, the respondent shall, before the expiration of 30 days from service of the complaint, file a request for an extension of time within which to file an answer that meets the requirements of paragraph (b) of this section. The presiding officer may, for good cause shown, grant the respondent up to 30 additional days within which to file an answer that meets the requirements of paragraph (b) of this section.

(d) The respondent may, on motion, amend its answer to conform with the evidence as justice may require.

§ 17.11 Default upon failure to file an answer.

(a) If the respondent does not file an answer within the time prescribed in § 17.9 and if service has been effected as provided in § 17.7, the presiding officer shall assume the facts alleged in the complaint to be true, and, if such facts establish liability under

the relevant statute, the presiding officer shall issue an initial decision within 30 days of the time the answer was due, imposing:

(1) The maximum amount of penalties provided for by law for the violations alleged; or

(2) The amount asked for in the complaint, whichever amount is smaller.

(b) Except as otherwise provided in this section, by failing to file a timely answer, the respondent waives any right to a hearing and to contest the amount of the penalties and assessments imposed under paragraph (a) of this section, and the initial decision shall become final and binding upon the parties 30 days after it is issued.

(c) If, before such a decision becomes final, the respondent files a motion seeking to reopen on the grounds that extraordinary circumstances prevented the respondent from filing an answer, the initial decision shall be stayed pending a decision on the motion.

(d) If, on such motion, the respondent can demonstrate extraordinary circumstances excusing the failure to file an answer in a timely manner, the presiding officer may withdraw the decision under paragraph (a) of this section, if such a decision has been issued, and shall grant the respondent an opportunity to answer the complaint as provided in § 17.9(a).

(e) If the presiding officer decides that the respondent's failure to file an answer in a timely manner is not excused, he or she shall affirm the decision under paragraph (a) of this section, and the decision shall become final and binding upon the parties 30 days after the presiding officer issues the decision on the respondent's motion filed under paragraph (c) of this section.

§ 17.13 Notice of hearing.

After an answer has been filed, the Center shall serve a notice of hearing on the respondent. Such notice shall include:

(a) The date, time, and place of a prehearing conference, if any, or the date, time, and place of the hearing if there is not to be a prehearing conference;

(b) The nature of the hearing and the legal authority and jurisdiction under which the hearing is to be held;

(c) A description of the procedures for the conduct of the hearing;

(d) The names, addresses, and telephone numbers of the representatives of the government and of the respondent, if any; and

(e) Such other matters as the Center or the presiding officer deems appropriate.

§ 17.15 Parties to the hearing.

(a) The parties to the hearing shall be the respondent and the Center(s) with jurisdiction over the matter at issue. No other person may participate.

(b) The parties may at any time prior to a final decision by the entity deciding any appeal agree to a settlement of all or a part of the matter. The settlement agreement shall be filed in the docket and shall constitute complete or partial resolution of the administrative case as so designated by the settlement agreement. The settlement document shall be effective upon filing in the docket and need not be ratified by the presiding officer or the Commissioner of Food and Drugs.

(c) The parties may be represented by counsel, who may be present at the hearing.

§ 17.17 Summary decisions.

(a) At any time after the filling of a complaint, a party may move, with or without supporting affidavits (which, for purposes of this part, shall include declarations under penalty of perjury), for a summary decision on any issue in the hearing. The other party may, within 30 days after service of the motion, which may be extended for an additional 10 days for good cause, serve opposing affidavits or countermove for summary decision.

The presiding officer may set the matter for argument and call for the submission of briefs.

(b) The presiding officer shall grant the motion if the pleadings, affidavits, and other material filed in the record, or matters officially noticed, show that there is no genuine issue as to any material fact and that the party is entitled to summary decision as a matter of law.

(c) Affidavits shall set forth only such facts as would be admissible in evidence and shall show affirmatively that the affiant is competent to testify to the matters stated. When a motion for summary decision is made and supported as provided in this regulation, a party opposing the motion may not rest on mere allegations or denials or general descriptions of positions and contentions; affidavits or other responses must set forth specific facts showing that there is a genuine issue of material fact for the hearing.

(d) If, on motion under this section, a summary decision is not rendered on all issues or for all the relief asked, and if additional facts need to be developed, the presiding officer will issue an order specifying the facts that appear without substantial controversy and directing further evidentiary proceedings on facts still at issue. The facts specified not to be at issue shall be deemed established.

(e) Except as provided in § 17.18, a party may not obtain interlocutory review by the entity deciding the appeal (currently the DAB) of a partial summary decision of the presiding officer. A review of final summary decisions on all issues may be had through the procedure set forth in § 17.47.

§ 17.18 Interlocutory appeal from ruling of presiding officer.

(a) Except as provided in paragraph (b) of this section, rulings of the presiding officer may not be appealed before consideration on appeal of the entire record of the hearing.

(b) A ruling of the presiding officer is subject to interlocutory appeal to the entity deciding the appeal (currently the DAB) if the presiding officer certifies on the record or in writing that immediate review is necessary to prevent exceptional delay, expense, or prejudice to any participant, or substantial harm to the public interest.

(c) When an interlocutory appeal is made, a participant may file a brief on the appeal only if specifically authorized by the presiding officer or the entity deciding the appeal (currently the DAB), and if such authorization is granted, only within the period allowed by the presiding officer or the entity deciding the appeal. If a participant is authorized to file a brief, any other participant may file a brief in opposition, within the period allowed by the entity deciding the appeal (currently the DAB). The deadline for filing an interlocutory appeal is subject to the discretion of the presiding officer.

§ 17.19 Authority of the presiding officer.

(a) The presiding officer shall conduct a fair and impartial hearing, avoid delay, maintain order, and assure that a record of the proceeding is made.

(b) The presiding officer has the authority to:

(1) Set and change the date, time, and place of the hearing on reasonable notice to the parties;

(2) Continue or recess the hearing in whole or in part for a reasonable time;

(3) Require parties to attend conferences for settlement, to identify or simplify the issues, or to consider other matters that may aid in the expeditious disposition of the proceeding;

(4) Administer oaths and affirmations;

(5) Issue subpoenas requiring the attendance and testimony of witnesses and the production of evidence that relates to the matter under investigation;

(6) Rule on motions and other procedural matters;

(7) Regulate the scope and timing of discovery consistent with § 17.23;

(8) Regulate the course of the hearing and the conduct of the parties;

(9) Examine witnesses;

(10) Upon motion of a party for good cause shown, the presiding officer may allow a witness to be recalled for additional testimony;

(11) Receive, rule on, exclude, or limit evidence;

(12) Upon motion of a party or on the presiding officer's own motion, take official notice of facts;

(13) Upon motion of a party, decide cases, in whole or in part, by summary decision when there is no genuine issue of material fact;

(14) Conduct any conference, argument, or hearing on motions in person or by telephone;

(15) Consolidate related or similar proceedings or sever unrelated matters;

(16) Limit the length of pleadings;

(17) Waive, suspend, or modify any rule in this part if the presiding officer determines that no party will be prejudiced, the ends of justice will be served, and the action is in accordance with law;

(18) Issue protective orders pursuant to § 17.28; and

(19) Exercise such other authority as is necessary to carry out the responsibilities of the presiding officer under this part.

(c) The presiding officer does not have the authority to find Federal statutes or regulations invalid.

§ 17.20 Ex parte contacts.

No party or person (except employees of the presiding officer's office) shall communicate in any way with the presiding officer on any matter at issue in a case, unless on notice and opportunity for all parties to participate. This provision does not prohibit a person or party from inquiring about the status of a case or asking routine questions concerning administrative functions or procedures.

§ 17.21 Prehearing conferences.

- (a) The presiding officer may schedule prehearing conferences as appropriate.
- (b) Upon the motion of any party, the presiding officer shall schedule at least one prehearing conference at a reasonable time in advance of the hearing.
- (c) The presiding officer may use a prehearing conference to discuss the following:
 - (1) Simplification of the issues;
 - (2) The necessity or desirability of amendments to the pleadings, including the need for a more definite statement;
 - (3) Stipulations and admissions of fact as to the contents and authenticity of documents;
 - (4) Whether the parties can agree to submission of the case on a stipulated record;
 - (5) Whether a party chooses to waive appearance at an oral hearing and to submit only documentary evidence (subject to the objection of the other party) and written argument;
 - (6) Limitation of the number of witnesses;
 - (7) Scheduling dates for the exchange of witness lists and of proposed exhibits;
 - (8) Discovery and scheduling dates for completion of discovery;
 - (9) The date, time, and place for the hearing; and
 - (10) Such other matters as may tend to expedite the fair and just disposition of the proceedings.
- (d) The presiding officer shall issue an order containing all matters agreed upon by the parties or ordered by the presiding officer at a prehearing conference.

§ 17.23 Discovery.

- (a) No later than 60 days prior to the hearing, unless otherwise ordered by the presiding officer, a party may make a request to another party for production, inspection, and copying of documents that are relevant to the issues before the presiding officer. Documents must be provided no later than 30 days after the request has been made.
- (b) For the purpose of this part, the term “documents” includes information, reports, answers, records, accounts, papers and other data and documentary evidence. Nothing contained in this section may be interpreted to require the creation of a document, except that requested data stored in an electronic data storage system must be produced in a form readily accessible to the requesting party.
- (c) Requests for documents, requests for admissions, written interrogatories, depositions, and any forms of discovery, other than those permitted under paragraphs (a) and (e) of this section, are not authorized.
- (d)(1) Within 10 days of service of a request for production of documents, a party may file a motion for a protective order.
- (2) The presiding officer may grant a motion for a protective order, in whole or in part, if he or she finds that the discovery sought:
 - (i) Is unduly costly or burdensome,
 - (ii) Will unduly delay the proceeding, or
 - (iii) Seeks privileged information.

(3) The burden of showing that a protective order is necessary shall be on the party seeking the order.

(4) The burden of showing that documents should be produced is on the party seeking their production.

(e) The presiding officer shall order depositions upon oral questions only upon a showing that:

(1) The information sought cannot be obtained by alternative methods, and

(2) There is a substantial reason to believe that relevant and probative evidence may otherwise not be preserved for presentation by a witness at the hearing.

§ 17.25 Exchange of witness lists, witness statements, and exhibits.

(a) At least 30 days before the hearing, or by such other time as is specified by the presiding officer, the parties shall exchange witness lists, copies of prior written statements of proposed witnesses, and copies of proposed hearing exhibits, including written testimony.

(b)(1) If a party objects to the proposed admission of evidence not exchanged in accordance with paragraph (a) of this section, the presiding officer will exclude such evidence if he or she determines that the failure to comply with paragraph (a) of this section should result in its exclusion.

(2) Unless the presiding officer finds that extraordinary circumstances justified the failure to make a timely exchange of witness lists under paragraph (a) of this section, he or she must exclude from the party's hearing evidence the testimony of any witness whose name does not appear on the witness list.

(3) If the presiding officer finds that extraordinary circumstances existed, the presiding officer must then determine whether the admission of the testimony of any witness whose name does not appear on the witness lists exchanged under paragraph (a) of this section would cause substantial prejudice to the objecting party. If the presiding officer finds that there is not substantial prejudice, the evidence may be admitted. If the presiding officer finds that there is substantial prejudice, the presiding officer may exclude the evidence, or at his or her discretion, may postpone the hearing for such time as is necessary for the objecting party to prepare and respond to the evidence.

(c) Unless a party objects within 5 days prior to the hearing, documents exchanged in accordance with paragraph (a) of this section will be deemed to be authentic for the purpose of admissibility at the hearing.

§ 17.27 Hearing subpoenas.

(a) A party wishing to procure the appearance and testimony of any individual at the hearing may, when authorized by law, request that the presiding officer issue a subpoena.

(b) A subpoena requiring the attendance and testimony of an individual may also require the individual to produce documents at the hearing.

(c) A party seeking a subpoena shall file a written request therefor not less than 20 days before the date fixed for the hearing unless otherwise allowed by the presiding officer, upon a showing by the party of good cause. Such request shall specify any documents to be produced and shall designate the witnesses and describe the address and location thereof with sufficient particularity to permit such witnesses to be found.

(d) The subpoena shall specify the time and place at which the witness is to appear and any documents the witness is to produce.

(e) The party seeking the subpoena shall serve it in the manner prescribed for service of a complaint in § 17.7.

(f) If a party or the individual to whom the subpoena is directed believes a subpoena to be unreasonable, oppressive, excessive in scope, or unduly burdensome, or if it wishes to raise any other objection or privilege recognized by law, the party or individual may file a motion to quash the subpoena within 10 days after service or on or before the time specified in the subpoena for compliance if it is less than 10 days after service. Such a filing will state the basis for the motion to quash. The presiding officer may quash or modify the subpoena or order it implemented, as justice may require.

§ 17.28 Protective order.

(a) A party or a prospective witness may file a motion for a protective order with respect to discovery sought by a party or with respect to the hearing, seeking to limit the availability or disclosure of evidence.

(b) When issuing a protective order, the presiding officer may make any order which justice requires to protect a party or person from oppression or undue burden or expense, or to protect trade secrets or confidential commercial information, as defined in § 20.61 of this chapter, information the disclosure of which would constitute a clearly unwarranted invasion of personal privacy, or other information that would be withheld from public disclosure under 21 CFR part 20. Such orders may include, but are not limited to, one or more of the following:

(1) That the discovery not be had;

(2) That the discovery may be had only on specified terms and conditions, including a designation of the time or place;

(3) That the discovery may be had only through a method of discovery provided for by this part other than that requested;

(4) That certain matters not be inquired into, or that the scope of discovery be limited to certain matters;

(5) That the contents of discovery or evidence be sealed;

(6) That the information not be disclosed to the public or be disclosed only in a designated way; or

(7) That the parties simultaneously file specified documents or information enclosed in sealed envelopes to be opened as directed by the presiding officer.

§ 17.29 Fees.

The party requesting a subpoena shall pay the cost of the fees and mileage of any witness subpoenaed in the amounts that would be payable to a witness in a proceeding in a United States District Court. A check for witness fees and mileage shall accompany the subpoena when served.

§ 17.30 Computation of time.

(a) In computing any period of time under this part or in an order issued thereunder, the time begins with the day following the act or event, and includes the last day of the

period, unless either such day is a Saturday, Sunday, or Federal holiday, in which event the time includes the next business day.

(b) When the period of time allowed is less than 7 days, intermediate Saturdays, Sundays, and Federal holidays shall be excluded from the computation.

(c) When a document has been served or issued by placing it in the mail, an additional 5 days will be added to the time permitted for any response.

§ 17.31 Form, filing, and service of papers.

(a) *Form.* (1) Documents filed with the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857, shall include an original and two copies.

(2) The first page of every pleading and paper filed in the proceeding shall contain a caption setting forth the title of the action, the case number assigned by the Office of the Chief Counsel, and designation of the pleading or paper (e.g., “motion to quash subpoena”).

(3) Every pleading shall be signed by, and shall contain the address and telephone number of, the party or the person on whose behalf the pleading was filed, or his or her counsel.

(4) Pleadings or papers are considered filed when they are received by the Dockets Management Branch.

(b) *Service.* A party filing a document with the Dockets Management Branch under this part shall, no later than the time of filing, serve a copy of such document on every other party. Service upon any party of any document, other than service of a complaint, shall be made by delivering a copy personally or by placing a copy of the document in the United States mail or express delivery service, postage prepaid and addressed, to the party’s last known address. When a party is represented by counsel, service shall be made on such counsel in lieu of the actual party.

(c) *Proof of service.* A certificate of the individual serving the document by personal delivery or by mail, setting forth the time and manner of service, shall be proof of service.

§ 17.32 Motions.

(a) Any application to the presiding officer for an order or ruling shall be by motion. Motions shall state the relief sought, the authority relied upon, and the facts alleged, and shall be filed with the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857, delivered to the presiding officer, and served on all other parties.

(b) Except for motions made during a prehearing conference or at the hearing, all motions shall be in writing. The presiding officer may require that oral motions be reduced to writing.

(c) Within 15 days after a written motion is served, or such other time as may be fixed by the presiding officer, any party may file a response to such motion.

(d) The presiding officer may not grant a written motion before the time for filing responses thereto has expired, except upon consent of the parties or following a hearing on the motion, but may overrule or deny such motion without awaiting a response.

§ 17.33 The hearing and burden of proof.

(a) The presiding officer shall conduct a hearing on the record to determine whether the respondent is liable for a civil money penalty and, if so, the appropriate amount of any such civil money penalty considering any aggravating or mitigating factors.

(b) In order to prevail, the Center must prove respondent's liability and the appropriateness of the penalty under the applicable statute by a preponderance of the evidence.

(c) The respondent must prove any affirmative defenses and any mitigating factors by a preponderance of the evidence.

(d) The hearing shall be open to the public unless otherwise ordered by the presiding officer, who may order closure only to protect trade secrets or confidential commercial information, as defined in § 20.61 of this chapter, information the disclosure of which would constitute a clearly unwarranted invasion of personal privacy, or other information that would be withheld from public disclosure under part 20 of this chapter.

§ 17.34 Determining the amount of penalties and assessments.

(a) When determining an appropriate amount of civil money penalties and assessments, the presiding officer and the Commissioner of Food and Drugs or entity designated by the Commissioner to decide the appeal (currently the DAB) shall evaluate any circumstances that mitigate or aggravate the violation and shall articulate in their opinions the reasons that support the penalties and assessments imposed.

(b) The presiding officer and the entity deciding the appeal shall refer to the factors identified in the statute under which the penalty is assessed for purposes of determining the amount of penalty.

(c) Nothing in this section shall be construed to limit the presiding officer or the entity deciding the appeal from considering any other factors that in any given case may mitigate or aggravate the offense for which penalties and assessments are imposed.

§ 17.35 Sanctions.

(a) The presiding officer may sanction a person, including any party or counsel for:

(1) Failing to comply with an order, subpoena, rule, or procedure governing the proceeding;

(2) Failing to prosecute or defend an action; or

(3) Engaging in other misconduct that interferes with the speedy, orderly, or fair conduct of the hearing.

(b) Any such sanction, including, but not limited to, those listed in paragraphs (c), (d), and (e) of this section, shall reasonably relate to the severity and nature of the failure or misconduct.

(c) When a party fails to comply with a discovery order, including discovery and subpoena provisions of this part, the presiding officer may:

(1) Draw an inference in favor of the requesting party with regard to the information sought:

(2) Prohibit the party failing to comply with such order from introducing evidence concerning, or otherwise relying upon, testimony relating to the information sought; and

(3) Strike any part of the pleadings or other submissions of the party failing to comply with such request.

(d) The presiding officer may exclude from participation in the hearing any legal counsel, party, or witness who refuses to obey an order of the presiding officer. In the case of repeated refusal, the presiding officer may grant judgment to the opposing party.

(e) If a party fails to prosecute or defend an action under this part after service of a notice of hearing, the presiding officer may dismiss the action or may issue an initial decision imposing penalties and assessments.

(f) The presiding officer may refuse to consider any motion, request, response, brief, or other document that is not filed in a timely fashion or in compliance with the rules of this part.

(g) Sanctions imposed under this section may be the subject of an interlocutory appeal as allowed in § 17.18(b), provided that no such appeal will stay or delay a proceeding.

§ 17.37 Witnesses.

(a) Except as provided in paragraph (b) of this section, testimony at the hearing shall be given orally by witnesses under oath or affirmation.

(b) Direct testimony shall be admitted in the form of a written declaration submitted under penalty of perjury. Any such written declaration must be provided to all other parties along with the last known address of the witness. Any prior written statements of witnesses proposed to testify at the hearing shall be exchanged as provided in § 17.25(a).

(c) The presiding officer shall exercise reasonable control over the manner and order of questioning witnesses and presenting evidence so as to:

(1) Make the examination and presentation effective for the ascertainment of the truth;

(2) Avoid undue consumption of time; and

(3) Protect witnesses from harassment or undue embarrassment.

(d) The presiding officer shall permit the parties to conduct such cross-examination as may be required for a full disclosure of the facts.

(e) At the discretion of the presiding officer, a witness may be cross-examined on relevant matters without regard to the scope of his or her direct examination. To the extent permitted by the presiding officer, a witness may be cross-examined on relevant matters with regard to the scope of his or her direct examination. To the extent permitted by the presiding officer, cross-examination on matters outside the scope of direct examination shall be conducted in the manner of direct examination and may proceed by leading questions only if the witness is a hostile witness, an adverse party, or a witness identified with an adverse party.

(f) Upon motion of any party, the presiding officer may order witnesses excluded so that they cannot hear the testimony of the other witnesses. This rule does not authorize exclusion of:

(1) A party who is an individual;

(2) In the case of a party that is not an individual, an officer or employee of the party designated to be the party's sole representative for purposes of the hearing; or

(3) An individual whose presence is shown by a party to be essential to the presentation of its case, including an individual employed by a party engaged in assisting counsel for the party.

(g) If a witness' testimony is submitted in writing prior to cross-examination, the

cross-examining party need not subpoena the witness or pay for his or her travel to the hearing. The sponsoring party is responsible for producing the witness at its own expense, and failure to do so shall result in the striking of the witness' testimony.

§ 17.39 Evidence.

(a) The presiding officer shall determine the admissibility of evidence.

(b) Except as provided in this part, the presiding officer shall not be bound by the "Federal Rules of Evidence." However, the presiding officer may apply the "Federal Rules of Evidence" when appropriate, e.g., to exclude unreliable evidence.

(c) The presiding officer shall exclude evidence that is not relevant or material.

(d) Relevant evidence may be excluded if its probative value is substantially outweighed by the danger of unfair prejudice, confusion of the issues, or by considerations of undue delay or needless presentation of cumulative evidence.

(e) Relevant evidence may be excluded if it is privileged under Federal law.

(f) Evidence of furnishing or offering or promising to furnish, or accepting or offering or promising to accept, a valuable consideration in settling or attempting to settle a civil money penalty assessment which was disputed as to either validity or amount, is not admissible to prove liability for or invalidity of the civil money penalty or its amount. Evidence of conduct or statements made in settlement negotiations is likewise not admissible. This rule does not require the exclusion of any evidence otherwise discoverable merely because it is presented in the course of settlement negotiations. This rule also does not require exclusion when the evidence is offered for another purpose, such as proving bias or prejudice of a witness or opposing a contention of undue delay.

(g) The presiding officer may in his or her discretion permit the parties to introduce rebuttal witnesses and evidence.

(h) All documents and other evidence offered or taken for the record shall be open to examination by all parties, unless otherwise ordered by the presiding officer pursuant to § 17.28.

§ 17.41 The administrative record.

(a) The hearing will be recorded and transcribed. Witnesses, participants, and counsel have 30 days from the time the transcript becomes available to propose corrections in the transcript of oral testimony. Corrections are permitted only for transcription errors. The presiding officer shall promptly order justified corrections. Transcripts may be obtained following the hearing from the Dockets Management Branch at a cost not to exceed the actual cost of duplication.

(b) The transcript of testimony, exhibits, and other evidence admitted at the hearing and all papers and requests filed in the proceeding constitute the administrative record for the decision by the presiding officer and the entity designated by the Commissioner of Food and Drugs to decide the appeal, currently the DAB.

(c) The administrative record may be inspected and copied (upon payment of a reasonable fee) by anyone unless otherwise ordered by the presiding officer, who shall upon motion of any party order otherwise when necessary to protect trade secrets or confidential commercial information, as defined in § 20.61 of this chapter, information the disclosure of which would constitute a clearly unwarranted invasion of personal privacy, or other information that would be withheld from public disclosure under part 20.

§ 17.43 Posthearing briefs.

Any party may file a posthearing brief. The presiding officer shall fix the time for filing such briefs (which shall be filed simultaneously), which shall not exceed 60 days from the date the parties received the transcript of the hearing or, if applicable, the stipulated record. Such briefs may be accompanied by proposed findings of fact and conclusions of law. The presiding officer may permit the parties to file responsive briefs. No brief may exceed 30 pages (exclusive of proposed findings and conclusions) unless the presiding officer has previously found that the issues in the proceeding are so complex, or the administrative record is so voluminous, as to justify longer briefs, in which case the presiding officer may set a longer page limit. Proposed findings of fact and conclusions of law shall not exceed 30 pages unless the presiding officer has previously found that the issues in the proceeding are so complex, or the administrative record is so voluminous, as to justify longer proposed findings and conclusions, in which case the presiding officer may set a longer page limit.

§ 17.45 Initial decision.

(a) The presiding officer shall issue an initial decision based only on the administrative record. The decision shall contain findings of fact, conclusions of law, and the amount of any penalties and assessments imposed.

(b) The findings of fact shall include a finding on each of the following issues:

(1) Whether the allegations in the complaint are true, and, if so, whether respondent's actions identified in the complaint violated the law;

(2) Whether any affirmative defenses are meritorious; and

(3) If the respondent is liable for penalties or assessments, the appropriate amount of any such penalties or assessments, considering any mitigating or aggravating factors that he or she finds in the case.

(c) The presiding officer shall serve the initial decision or the decision granting summary decision on all parties within 90 days after the time for submission of posthearing briefs and responsive briefs (if permitted) has expired. If the presiding officer believes that he or she cannot meet the 90-day deadline, he or she shall notify the Commissioner of Food and Drugs or other entity designated by the Commissioner to decide the appeal of the reason(s) therefor, and the Commissioner or that entity may then set a new deadline.

(d) Unless the initial decision or the decision granting summary decision of the presiding officer is timely appealed, the initial decision or the decision granting summary decision shall constitute the final decision of FDA and shall be final and binding on the parties 30 days after it is issued by the presiding officer.

§ 17.47 Appeals.

(a) Either the Center or any respondent may appeal an initial decision, including a decision not to withdraw a default judgment, or a decision granting summary decision to the Commissioner of Food and Drugs or other entity the Commissioner designates to decide the appeal. The Commissioner has currently designated the Departmental Appeals Board (DAB) to decide appeals under this part. Parties may appeal to the DAB by filing a notice of appeal with the DAB, rm. 637-D, Hubert H. Humphrey Bldg., 200 Independence Ave. SW., Washington, DC 20201, and the Dockets Management Branch (HFA-

305), Food and Drug Administration, rm. 1–23, 12420 Parklawn Dr., Rockville, MD 20857, in accordance with this section.

(b)(1) A notice of appeal may be filed at any time within 30 days after the presiding officer issues an initial decision or decision granting summary decision.

(2) The Commissioner or the entity designated by the Commissioner to hear appeals may, within his or her discretion, extend the initial 30-day period for an additional period of time if the Center or any respondent files a request for an extension within the initial 30-day period and shows good cause.

(c) A notice of appeal shall be accompanied by a written brief of no greater length than that allowed for the posthearing brief. The notice must identify specific exceptions to the initial decision, must support each exception with citations to the record, and must explain the basis for each exception.

(d) The opposing party may file a brief of no greater length than that allowed for the posthearing brief in opposition to exceptions within 30 days of receiving the notice of appeal and accompanying brief, unless such time period is extended by the Commissioner or the entity designated by the Commissioner to hear appeals on request of the opposing party for good cause shown. Any brief in opposition to exceptions shall be filed with the Dockets Management Branch and the DAB (addresses above).

(e) The appellant may file a reply brief not more than 10 pages in length within 10 days of being served with appellee's brief.

(f) There is no right to appear personally before the Commissioner of Food and Drugs or other entity deciding the appeal (currently the DAB).

(g) The entity deciding the appeal will consider only those issues raised before the presiding officer, except that the appellee may make any argument based on the record in support of the initial decision or decision granting summary decision.

(h) If on appeal the entity deciding the appeal considers issues not adequately briefed by the parties, the entity may ask for additional briefing. However, no such additional briefs will be considered unless so requested.

(i) If any party demonstrates to the satisfaction of the entity deciding the appeal (currently the DAB) that additional evidence not presented at the hearing is relevant and material and that there were reasonable grounds for the failure to adduce such evidence at the hearing, the entity deciding the appeal may remand the matter to the presiding officer for consideration of the additional evidence.

(j) The Commissioner of Food and Drugs or other entity deciding the appeal (currently the DAB) will issue a decision on the appeal within 60 days, if practicable, of the due date for submission of the appellee's brief. In the decision, the entity deciding the appeal may decline to review the case, affirm the initial decision or decision granting summary decision (with or without an opinion), or reverse the initial decision or decision granting summary decision, or increase, reduce, reverse, or remand any civil money penalty determined by the presiding officer in the initial decision. If the entity deciding the appeal declines to review the case, the initial decision or the decision granting summary decision shall constitute the final decision of FDA and shall be final and binding on the parties 30 days after the declination by the entity deciding the appeal.

(k) The standard of review on a disputed issue of fact is whether the initial decision is supported by substantial evidence on the whole record. The standard of review on a disputed issue of law is whether the initial decision is erroneous.

§ 17.48 Harmless error.

No error in either the admission or the exclusion of evidence, and no error or defect in any ruling or order or in any act done or omitted by the presiding officer or by any of the parties is grounds for vacating, modifying, or otherwise disturbing an otherwise appropriate ruling or order or act, unless refusal to take such action appears to the presiding officer or the Commissioner of Food and Drugs or other entity deciding the appeal (currently the DAB) to be inconsistent with substantial justice. The presiding officer and the entity deciding the appeal at every stage of the proceeding will disregard any error or defect in the proceeding that does not affect the substantial rights of the parties.

§ 17.51 Judicial review.

(a) The final decision of the Commissioner of Food and Drugs or other entity deciding the appeal (currently the DAB) constitutes final agency action from which a respondent may petition for judicial review under the statutes governing the matter involved. Although the filing of a petition for judicial review does not stay a decision under this part, a respondent may file a petition for stay of such decision under § 10.35 of this chapter.

(b) The Chief Counsel of FDA has been designated by the Secretary of Health and Human Services as the officer on whom copies of petitions for judicial review are to be served. This officer is responsible for filing the record on which the final decision is based. The record of the proceeding is certified by the entity deciding the appeal (currently the DAB).

(c) Exhaustion of an appeal to the entity deciding the appeal (currently the DAB) is a jurisdictional prerequisite to judicial review.

§ 17.54 Deposit in the Treasury of the United States.

All amounts assessed pursuant to this part shall be delivered to the Director, Division of Financial Management (HFA-100), Food and Drug Administration, rm. 11-61, 5600 Fishers Lane, Rockville, MD 20857, and shall be deposited as miscellaneous receipts in the Treasury of the United States.

PART 20—PUBLIC INFORMATION

7. The authority citation for part 20 continues to read as follows:

Authority: Secs. 201–903 of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 321–393); secs. 301, 302, 303, 307, 310, 311, 351, 352, 354–360F, 361, 362, 1701–1706, 2101 of the Public Health Service Act (42 U.S.C. 241, 242, 242a, 242l, 242n, 243, 262, 263, 263b–263n, 264, 265, 300u–300u–5, 300aa–1); 5 U.S.C. 552; 18 U.S.C. 1905.

§ 20.86 [Amended]

8. Section 20.86 is amended by revising the first sentence to read as follows:

§ 20.86 Disclosure in administrative or court proceedings.

Data and information otherwise exempt from public disclosure may be revealed in Food and Drug Administration administrative proceedings pursuant to parts 10, 12, 13,

14, 15, 17, and 19 of this chapter or court proceedings, where data or information are relevant. * * *

Dated: July 12, 1995.

William B. Schultz,

Deputy Commissioner for Policy.

[FR Doc. 95-18325 Filed 7-26-95; 8:45 am]

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Appendix D

Section 601.12 Changes Currently Considered “Important” by CBER

The guidance document is not intended to affect the reporting requirements currently specified in Section 601.12, but to provide clarifying descriptions of the types of changes that are currently considered to be “important” within the meaning of that section. In addition, the document clarifies the types of changes that may be implemented 30 days after submission of a supplement and those that must await approval of a supplement prior to implementation. Thus, the guidance document outlines three categories for reporting changes, based on the importance and nature of the changes. The document lists examples of changes that would fall into each category.

This document does not apply to changes in manufacturing processes and facilities associated with the manufacture of whole blood, blood components, source leukocytes, or source plasma. CBER is currently evaluating reporting requirements in those areas. In addition, the guidance document does not address labeling changes. However, in the *Federal Register* of August 3, 1994 (59 FR 39570), FDA published a notice of availability for the revised Office of Establishment Licensing and Product Surveillance Advertising and Promotional Labeling Staff (APLS) Procedural Guidance Document. The APLS Procedural Guidance document details the approach that manufacturers and distributors should follow in submitting advertising and promotional material for review by CBER. The APLS Procedural Guidance Document also provides guidance on CBER’s current interpretation of Section 601.12 as it applies to reporting important proposed changes in labeling; specifically, promotional labeling of biological products for which a license is in effect or for which an application for a license is pending.

As with other guidance documents, FDA does not intend this document to be all inclusive. The document is intended to provide information and does not set forth require-

ments. Manufacturers may follow the guidance or may choose to use alternative procedures even though they are not provided in this document. If a manufacturer chooses to use alternative procedures, that manufacturer may wish to discuss the matter further with CBER to prevent expenditure of resources on activities that FDA may later determine to be unacceptable.

This guidance document is not binding on either FDA or licensed manufacturers of biological products and does not create or confer any rights, privileges, or benefits for or on any person.

Interested persons may submit to the Dockets Management Branch written comments on the guidance document. Received comments will be considered to determine if further revision to the guidance document is necessary.

The text of the guidance document follows:

FOOD AND DRUG ADMINISTRATION, CENTER FOR BIOLOGICS EVALUATION AND RESEARCH (CBER), CHANGES TO BE REPORTED FOR PRODUCT AND ESTABLISHMENT LICENSE APPLICATIONS; GUIDANCE

I. INTRODUCTION AND BACKGROUND

A significant number of supplements to approved biological product and establishment license applications submitted to CBER during an average year involve changes which fall under Sec. 601.12 Changes to be reported (21 CFR 601.12).

Under this regulation, important proposed changes in location, equipment, management and responsible personnel, or in manufacturing methods and labeling, are required to be reported to CBER not less than 30 days in advance of the time such changes are intended to be made (Sec. 601.12(a)). Proposed changes in manufacturing methods and labeling may not become effective until notification of acceptance is received from the Director, CBER (sec. 601.12 (b)).

This document is not intended to affect the reporting requirements in Sec. 601.12, but to provide clarifying descriptions of those requirements. This guidance does not apply to manufacturers of whole blood, blood components, source leukocytes, and source plasma. Guidance on reporting requirements in those areas is currently under evaluation within CBER. In addition, this document does not address labeling changes. For guidance on the submission of advertising and promotional material, see the Office of Establishment Licensing and Product Surveillance Advertising and Promotional Labeling Staff (APLS) Procedural Guidance Document (August 1994).

To facilitate the approval process, CBER performed a review of the types of changes being reported and assessed the relative impact of each change on product purity, potency, and safety. Results of this analysis have provided CBER the rationale for describing three categories of changes based on potential effect on product safety, purity, and potency, with each category associated with a different notification mechanism. In general, the types of changes for which CBER recommends less stringent reporting represent changes which, for the most part, have not been associated with demonstrable effects on product purity, potency, or safety, and/or which are readily amenable to on-site scrutiny during

inspection of the production facility. In many instances, manufacturers will need to evaluate changes addressed in the three categories using validated standard operating procedures (SOP's) or specifications.

Regardless of whether a supplement is required to be filed, the manufacturer in making such changes must conform to the current good manufacturing practice (CGMP) requirements of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 351 (a) (2) (B)) and the regulations in 21 CFR parts 210 and 211. Changes affecting the method of manufacture require validation under the CGMP regulations. In addition, manufacturers must comply with the recordkeeping requirements under the CGMP regulations and ensure that relevant records are readily available for FDA inspection.

This document identifies and categorizes the types of change in manufacturing processes and establishments which may be implemented with and without prior approval by CBER.

This guidance document is not binding on either FDA or licensed manufacturers of biological products and does not create or confer any rights, privileges, or benefits for or on any person. It does, however, describe CBER's current interpretation of Sec. 601.12. Where this document reiterates a requirement imposed by statute or regulation, the force and effect as law of the requirement is not changed in any way by virtue of its inclusion in this document.

Section A of this document contains general definitions of each category of change as it pertains to notification or reporting requirements outlined in Sec. 601.12 (a) and (b). This section also defines a Periodic Report for Category I changes. Section B of this document provides instruction on sending submissions to CBER. Section C of this document augments these definitions with selected examples of modifications appropriately falling under each category. Section D of this document contains guidance on categorizing proposed changes which may not be listed in section C. Section E of this document discusses the kind of information the agency is asking manufacturers to submit in a Periodic Report.

II. GUIDANCE AND RATIONALE

A. Definitions

General definitions of each category of reporting changes are as follows:

1. Category I—Change(s) for Which No Supplement Submission Is Required and Which May Be Described in a Periodic Report

This category includes modifications to procedures, process parameters, components, manufacturing methods, reagents, equipment and facilities which do not rise to the level of the "important" changes required to be reported under Sec. 601.12. These are changes that are designed to tighten control on the production process, or have not been associated with adverse impact on product safety, purity or potency. Manufacturers should qualify and, as necessary, validate such changes before implementing them. These changes should be shown not to affect the integrity of the product. For this category, the manufacturer generates and retains all relevant data defining (and, as necessary, validating) changes which are implemented. In order to expedite the agency's review of changes, such data

should be readily accessible for FDA-establishment inspections. The agency recommends that the firm notify CBER in a Periodic Report (see description below) of the changes and dates of implementation.

2. Category II—Change(s) Requiring a Supplement Submission and Which May Be Implemented Prior to CBER Approval

This category includes modifications to location, equipment, management, and personnel that do not change manufacturing methods, but have the potential to adversely affect product safety, purity, and potency. For these changes, the manufacturer should submit a standard supplement, accompanied by all relevant supporting data, with a request to implement not less than 30 days following the supplement's receipt by CBER's Document Control Center. Such supplements should be clearly marked "Category II Supplement, Changes to be Implemented" at the top of the cover letter. CBER will confirm the submission and its receipt date in the reference number assignment letter. CBER intends to follow relevant application review policies in assigning supplement review.

CBER will process Category II changes as establishment or product license application supplements and will take official action on such supplements on, before, or after this 30-day period. If CBER officials do not contact the sponsor via telephone or written correspondence within 30 days following the documented receipt date to question or reject the "Category II" status, the manufacturer may implement the change. CBER may communicate with the firm during this 30 day period for clarification or to advise that the change is considered to be a Category III supplement (see description below).

Manufacturers should be aware that Category II changes are implemented subject to agency approval. The agency may refuse to approve a supplement for a change that has already been implemented. In assessing a manufacturer's plans to correct a problem, the agency intends to consider the manufacturer's reasons for making the change and the alternatives available to the manufacturer, among other things. If the circumstances warrant, the agency may require the change to be immediately discontinued. When circumstances permit, it is FDA's intent to allow manufacturers to correct a problem with minimal expense and without unnecessary waste.

3. Category III—Change(s) Which Require CBER Approval Prior to Implementation

This category includes changes in manufacturing methods and requires manufacturers to submit all relevant supporting documentation and await CBER's approval prior to implementation. As with Category II submissions, CBER intends to follow relevant application review policies in assigning supplement review.

4. Periodic Reports

A Periodic Report is a voluntary written report submitted every 6 months listing and briefly describing describing Category I changes and providing the date of implementation of such changes. Reports should include separate descriptions of EACH change affecting a licensed product and should identify for each change the specific establishment location involved. (See section E of this document for requested information.)

B. Where to Submit Supplements and Periodic Reports

Three copies of all supplements and periodic reports should be submitted to the Center for Biologics Evaluation and Research (HFM-99), Food and Drug Administration, 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448.

C. Selected Examples

1. Category I

CBER currently considers the following examples to be changes that will not ordinarily rise to the level of the “important” changes required to be reported under Sec. 601.12. These changes need not be submitted to CBER prior to implementation and may be submitted in a periodic report as “Category I changes.” This listing provides representative samples of Category I changes and is not all inclusive.

i. Change in purchasing source of approved final fill components (stoppers, vials, seals) that meet established specifications. This does not include change(s) in composition of such components or suppliers of ancillary chemicals and drug products such as diluents.

ii. Change in harvesting and/or pooling procedures which does not affect method of manufacture, recovery, storage conditions, sensitivity of detection of adventitious agents, or production scale; e.g., collection in smaller quantities to improve process efficiency.

iii. Changes in cell inoculum; e.g., mode of expansion (attached versus suspension; bioreactor versus spinner), cell density, staging of culture. This excludes viral products; e.g., vaccines and in vitro diagnostic kits.

iv. Change in storage conditions of reference standard or panel based on stability data generated with an FDA-approved protocol.

v. Extension of dating period for in-house reference standards, based on real-time data, according to an FDA-approved protocol.

vi. Replacement of inhouse reference standard or reference panel (or panel member) according to FDA-approved standard operating procedures (SOP's) and specifications.

vii. Tightening of specifications for reference standard or lot release analyses.

viii. Establishment of new Working Cell Bank derived from previously approved Master Cell Bank according to an FDA-approved SOP.

ix. Narrowing (tightening) of specifications for intermediates and end-products to provide greater assurance of product purity and potency.

x. Use of alternative storage containers for intermediates, with no change in sterility, depyrogenation status, or composition of container.

xi. Change in storage conditions of inprocess intermediates based on data from an FDA-approved stability protocol (labeling not affected).

xii. Change in bulk pool size for formulation without process scale-up.

xiii. Batch size changes for ancillary components (specimen diluents, positive and/or negative controls, substrate buffers, etc.) where all equipment contact surfaces remain chemically identical to approved equipment.

xiv. Change in the number of vials per fill with no scale-up or impact on parameters defined in the environmental assessment.

xv. Change in shipping conditions (e.g., temperature, packaging, custody) based upon data derived from studies following an FDA-approved protocol.

xvi. Rework of biologic product which has failed final release testing using FDA-approved rework protocol. Note: Any lot of product subject to rework should be so noted on the product release protocol.

xvii. Change in stability test protocol to include more stringent parameters; e.g., additional assays, tightened specifications, etc.

xviii. Replacement of equipment with that of identical design and operating principle involving no change in process parameters.

xix. The following modifications of areas not used for production or, storage of intermediate or finished product (such as testing laboratories, materials storage, warehouse, employee break areas, etc.):

(a) Addition of outside areas that do not adversely affect the product manufacturing area or utility systems;

(b) Expansion or reorganization of off-site support space that does not affect the product manufacturing areas;

(c) Modification to or relocation of support space within a product manufacturing facility that does not affect plant utility systems and flow patterns, or adversely affect product purity or environmental conditions (e.g., addition of half partitions or benches).

xx. The relocation of equipment within appropriate areas of approved facilities, not increasing risk to product purity or integrity of testing (e.g., relocation of fermentor in fermentation suite).

xxi. Upgrade in air quality, material, or personnel flow where product specifications remain unchanged. Involves no change in equipment or physical structure of production area.

xxii. Changes in personnel other than the Responsible Head (21 CFR 600.10) or individuals serving in a capacity of alternative or temporary Responsible Head.

2. Category II

CBER currently considers the following examples to be “important” proposed changes in location, equipment, management and responsible personnel. These changes must be reported pursuant to Sec. 601.12 (a) and meet the definition of a “Category II Supplement.” This listing provides representative samples of Category II changes and is not all inclusive.

i. Addition of back-up systems for manufacturing processes which are identical to the primary system and serve as an alternate resource (not expansion of capacity) within an approved production area.

ii. Upgrade to production air handling or water systems using like equipment and not affecting established specifications; e.g., removal of dead legs in water for injection (WFI) system. (Does not include replacement of parts or routine repair and maintenance (Category I).)

iii. Replacement of equipment with that of similar, but not identical, design and operating principle that does not affect the process methodology.

iv. Expansion of existing manufacturing support systems (WFI, heating, ventilation, and air-conditioning (HVAC)); e.g., adding an additional WFI loop.

v. Relocation of operations within the same production area of an approved facility with no change in equipment or room classification.

vi. Modification of an approved manufacturing area which does not adversely affect safety, purity or potency of product; e.g., adding new interior partitions or walls to increase control over the environment and replacing or adding new surfaces to enhance cleaning.

vii. Change in Responsible Head (21 CFR 600.10) or individuals serving in a capacity of alternative or temporary Responsible Head.

3. Category III

CBER currently considers the following examples to be “important” proposed changes in manufacturing methods. These changes require CBER approval before they

may be implemented under Sec. 601.12 (b), and meet the definition of a “Category III Supplement.” This listing provides representative samples of Category III changes and is not all inclusive.

- i. Establishment of new Master Cell Bank.
- ii. Change in inhouse reference standard or reference panel (panel member) resulting in modification of reference specifications.
- iii. Establishment of alternate test method for reference standards, release panels, product intermediates, or endproduct.
- iv. Replacement of existing test method with new procedure or method; e.g., change from radioimmunoassay (RIA) to enzyme-linked immunosorbent assay (ELISA).
- v. Change in process parameters; e.g., growth cycle, chromatographic medium, process time and/or temperature, filtration process.
- vi. Change in sequence of processing steps, including addition of processing step; e.g., viral removal or inactivation.
- vii. Change in production scale (up or down) involving changes in equipment, process parameters, or process methodology.
- viii. Change in chemistry or formulation of solutions used during processing.
- ix. Changes in conjugation chemistry or process.
- x. Changes in composition of the biological product or ancillary components.
- xi. Change in dosage form.
- xii. Any change which results in detectable relaxing of product specifications and modification in potency, sensitivity, or specificity.
- xiii. Change in fill volume (per vial) from an approved production batch size and/or scale.
- xiv. Reprocessing of product without a previously approved reprocessing protocol.
- xv. Change in stability testing program; e.g., substitution of analytical methods or potency assay, broadening of acceptance criteria, change in storage temperature, change in test algorithm.
- xvi. Extension of dating period for intermediate or endproduct.
- xvii. Change in storage conditions for licensed final product or intermediate based on real-time data from FDA-approved stability protocol (labeling affected).
- xviii. The following changes in manufacturing location that affect process conditions and thereby have the potential to affect product safety, purity, or potency:
 - (a) Use of a previously unapproved manufacturing area or facility;
 - (b) Change in air quality, water quality, material, or personnel flow for licensed product manufacturing areas.
 - (c) Change from single product manufacturing to multiple product manufacturing using same equipment and/or personnel.
 - (d) Renovation to physical structure that alters product, material, and/or personnel flow.
- xix. Addition to or replacement of an FDA-approved manufacturing step performed under contract to a second facility.

D. Categorization of Proposed Changes

Before implementing a change which is not identified above or does not clearly fit into one of the defined categories, manufacturers should discuss the proposed

change with CBER. If guidance is not sought, the change should be reported in the form of a Category III supplement, subject to CBER approval prior to implementation.

Requests for information regarding categorization of proposed changes not included in the above categories may be addressed to the Director of the appropriate applications Division within the Office with assigned product, or establishment, responsibility at the Center for Biologics Evaluation and Research (HFM-99), Food and Drug Administration, 1401 Rockville Pike, suite 200N, Rockville, MD 20852-1448.

E. Information Requested for Category I Periodic Reports

FDA requests that manufacturers submit the following information for each Category I change in the order shown: (1) Name of the manufacturer; (2) the establishment license number; (3) the report dates (time period covered by the report); (4) the product(s) affected (list each one); (5) the change implemented, including: (a) A brief description and reason for the change and/or modification, (b) the establishment location involved, (c) the date the change was implemented, and (d) a cross-reference to the Approved Validation Protocol or Standard Operating Procedure, if applicable; and (6) the signature of the Responsible Head and the date signed.

Dated: March 31, 1995

William B. Schultz

Deputy Commissioner for Policy

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 312, 314, and 320

[Docket No. 89N-0367]

RIN 0905-AC94

Retention of Bioavailability and Bioequivalence Testing Samples

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing final regulations to amend its current bioavailability/bioequivalence regulations to require the retention for a specified period of reserve samples of the drug products used to conduct certain bioavailability or bioequivalence studies submitted in support of the approval of new drug applications (NDA's) and abbreviated new drug applications (ANDA's), and when specifically requested, to release the reserve samples of FDA. The requirement applies to manufacturers who conduct in-house bioavailability and bioequivalence testing and to testing facilities who conduct such testing under contract for a drug manufacturer. The requirement also applies to foreign manufacturers who conduct their own studies for new drug product approval and to foreign testing facilities under contract for a U.S. manufacturer or foreign manufacturer. This action is intended to help ensure bioequivalence between generic drugs and their brand-name counterparts and to help the agency investigate more fully instances of possible fraud in bioavailability and bioequivalence testing. This final rule adopts the interim rule published in the **Federal Register** of November 8, 1990, with minor changes based on comments the agency received on the interim rule.

DATES: Effective May 28, 1993. Submit information on the Economic Impact section of this document (section III.) by May 28, 1993.

ADDRESSES: Submit information on the Economic Impact section of this document to the Dockets Management Branch (HFA-305) Food and Drug Administration, rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Marilyn L. Watson, Center for Drug Evaluation and Research (HFD-360), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-295-8038.

SUPPLEMENTARY INFORMATION: In the **Federal Register** of November 8, 1990 (55 FR 47034), FDA published interim regulations to require the retention for a specified period of reserve samples of the drug products used to conduct bioavailability or bioequivalence studies of drug products, and when specifically requested, to release the reserve samples to FDA. The interim regulations were effective on the date of publication. FDA provided 60 days for public comment. The final rule incorporates all of the main provisions of the interim rule; the agency has made a number of minor clarifying changes in response to the comments received on the interim rule.

Highlights of the final rule are summarized below, followed by a summary and discussion of the comments.

I. Highlights of the Final Rule

In the November 8, 1990, interim rule, the agency codified requirements regarding the retention of bioavailability and bioequivalence testing samples as part of the bioavailability/bioequivalence regulations existing at that time by adding §§ 320.32 and 320.63 (21 CFR 320.32 and 320.63), and by adding conforming amendments to § 320.31 (21 CFR 320.31) and to FDA's investigational new drug application (IND) and NDA regulations, new §§ 312.57(c), 314.125(b)(17), and 314.150(b)(9) (21 CFR 312.57(c), 314.125(b)(17), and 314.150(b)(9)). The purpose of these new requirements is to make available to FDA reserve samples of tested products for analysis to ensure that the bioequivalence and bioavailability results upon which FDA bases approval of NDA's and ANDA's are reliable. The rule also permits the agency the discretion to refuse to approve and to withdraw approval of an application if an applicant or testing laboratory refuses to permit an inspection of the facilities or records relevant to a bioavailability or bioequivalence study or to release to FDA reserve samples when requested.

In the **Federal Register** of July 10, 1989 (54 FR 28872 at 28911), FDA proposed changes in the regulations in existing 21 CFR part 320. Those proposed changes would, among other things, remove subpart C and those regulations that apply to establishing a bioequivalence requirement, move to subpart B the remaining regulations under existing subpart C, and where appropriate, combine the remaining regulations with the existing subpart B regulations. In the **Federal Register** of April 28, 1992 (57 FR 17950 at 17997), the proposed new subpart B structure was issued as a final rule. The agency is now conforming this rule to the new subpart B structure.

A. *Scope*

The final rule applies to domestic and foreign sponsors and applicants (hereinafter called a study sponsor) who perform in-house bioavailability or bioequivalence testing for new drug product approval under an NDA, ANDA, or supplemental application and

to any domestic and foreign testing facility that performs such bioavailability or bioequivalence testing under contract (contract research organization) for a study sponsor.

B. Sample Retention Requirement

A study sponsor or contract research organization, whoever performs bioavailability or bioequivalence testing for new drug product approval, must retain a reserve sample of each test article and reference standard used to perform in vivo bioavailability or in vivo or in vitro bioequivalence studies that is representative of each batch of the test article and of the reference standard provided by the study sponsor for the testing. The final rule clarifies the types of in vivo bioavailability and bioequivalence studies for which reserve samples are to be retained. The study sponsor or contract research organization will retain a sufficient quantity of each reserve sample of the test article and of the reference standard to permit FDA to perform five times all of the release tests required in the NDA, ANDA, or supplemental application. In addition, each reserve sample is required to be: (1) Adequately identified so that it can be positively identified as having come from the same sample as used in the specific bioavailability or bioequivalence study, (2) stored under specified conditions, and (3) retained for a specified period. An ambiguity in the interim rule regarding storage conditions has been clarified to accurately reflect the agency's intent. In addition, the final rule also includes a provision for the transfer of reserve samples when a contract research organization goes out of business.

C. Collection of Samples

Ordinarily, the reserve samples, or a portion of the reserve samples, will be collected by an FDA investigator at the place of storage during a preapproval inspection of the facilities involved in manufacturing the test article and of any contract testing facility that conducts bioavailability or bioequivalence testing for the study sponsor. Where FDA has reason to believe fraud was involved in performing a bioavailability or bioequivalence study that was conducted by a foreign testing facility, the facility may be asked to consent to FDA inspection or to submit to FDA reserve samples of the products used in the study.

Because access to test samples and related records may be essential to assess the validity and reliability of the results of a required bioavailability or bioequivalence study, the final rule, like the interim rule, adds as a reason for refusing to approve an application and as a circumstance under which FDA has discretion to withdraw approval of an application, refusal to permit an inspection of the facilities or records relevant to a bioavailability or bioequivalence study contained in an application or to submit or release reserve samples when requested by the agency.

II. Comments

FDA received 27 comments on the interim rule. The comments came from pharmaceutical manufacturers, trade associations, a professional group, and contract testing facilities. Most of the comments raised questions or concerns about the reserve sample retention period, quantity of the samples to be retained, and storage requirements for the samples. Several comments requested clarification of the types of in vivo bioavailability studies for which test samples would have to be retained under the new rule. Comments also were received in response to the agency's questions about whether additional requirements

were necessary to ensure that the integrity of the reserve samples is not compromised during the retention period.

A. Definition of an “NDA Biobatch” and an “ANDA Biobatch”

1. A number of comments requested clarification of the types of bioavailability studies from which test samples would have to be retained. The comments asked whether the many types of clinical pharmacology, pharmacokinetic, and pharmacodynamic studies in which blood samples are routinely collected for analysis would be considered bioavailability studies for purposes of this rule. Some of the comments suggested that reserve samples be retained only from studies which define the absolute or relative bioavailability of a new drug and studies necessary to demonstrate the bioequivalence of a new formulation to that which was previously studied in clinical trials.

One comment asserted that sample retention should be limited to the lot of test and reference formulations used in the pivotal bioequivalence study. The comment stated that, in the case of an NDA, this would be the lot of the product used in the study or studies conducted to demonstrate equivalence between the investigational formulation(s) and the formulation proposed for marketing. For an ANDA or supplemental application, this would be the study conducted to demonstrate equivalence between the currently marketed form and that proposed for marketing.

Two comments asked whether reserve samples should be kept for all in vivo “bio-studies,” whether or not the studies were submitted in support of the approval of an application or only for those studies required for approval of an application. The comments’ question was based on a perceived conflict between the language of the interim rule at § 320.32(a) (requires retention of samples used in an in vivo bioavailability study “required for approval of the application or supplemental application”), §§ 312.57(c) and 320.31(d)(1) (requires sponsors of all IND’s for “biostudies” and persons conducting such studies under an exemption from the IND requirements to retain samples of the products tested, “in accordance with * * * § 320.32”), and § 320.63 (retention of samples is required for products used in an in vivo or in vitro bioequivalence study “required for approval of, or submitted in support of the approval of, the full or abbreviated application or supplemental application * * * in accordance with * * * § 320.32.” The comments further asked whether the requirements apply to in vitro studies, noting that § 320.63 refers to sample retention for certain in vitro studies in accordance with § 320.32, but § 320.32 does not apply to in vitro studies.

The agency’s Compliance Program 7346.832¹ defines “NDA biobatches” as those NDA batches comparing the product planned for marketing with that studied during clinical trials to establish their equivalence. Generic product biobatches are ANDA batches that are compared to the originator/reference product to establish their equivalence. (See Compliance Program 7346.832, Part III, page 2, footnote 2.) Consistent with these definitions, the final rule applies to the following types of bioavailability/bioequivalence studies:

a. *NDA.* (i) If the formulation of the applicant’s proposed drug product (test article) is the same as the formulation(s) used in the pivotal clinical studies, the applicant would

¹ Compliance Program 7346.832 is available at cost from the Freedom of Information Staff (HFI-35). Food and Drug Administration, rm. 12A-30, 5600 Fishers Lane, Rockville, MD 20857

retain a reserve sample from the batch of the test article used to conduct an in vivo bioavailability study comparing the test article to a reference oral solution, suspension, or injection. A reserve sample of the reference standard (oral solution, suspension, or injection), which is usually made up when needed for a study, would not be retained. If the bioavailability study needs to be repeated, the reference standard would be prepared at the time of the study. For purposes of this rule, pivotal clinical studies are those adequate and well-controlled studies necessary to establish the safety and effectiveness of the test article for its claimed indications.

(ii) If the formulation of the test article differs from the formulation(s) used in conducting the pivotal clinical studies, the applicant would retain a reserve sample of the test article and of the reference standard from the batches used to conduct an in vivo bioequivalence study comparing the test article to the formulation(s) (reference standard) used in the pivotal clinical studies.

(iii) For a new formulation, new dosage form, or a new salt or ester of an active drug ingredient or therapeutic moiety that has been approved for marketing, a reserve sample of the test article and of the reference standard would be retained from the batches used to conduct an in vivo bioequivalence study comparing the test article to a marketed product (reference standard) that contains the same active drug ingredient or therapeutic moiety.

For an NDA, test article means the drug product for which the applicant is seeking approval. Reference standard has the same meaning as the term reference material in § 320.25.

b. *ANDA*. Reserve samples of the test article and reference standard would be retained from those batches used to conduct an in vivo bioavailability or an in vitro study comparing the test article to the approved drug product upon which the applicant relies for approval of its proposed product to establish their equivalence.

For an ANDA, test article means the drug product for which the applicant is seeking approval. Reference standard means an approved drug product identified by FDA as the drug product upon which an applicant relies in seeking approval of its ANDA and is usually the innovator product.

The agency has revised the final rule at §§ 312.57(c) and 320.38 (§ 320.32 in the interim rule) to clarify the in vivo bioavailability studies from which reserve samples are to be retained. With respect to the reference to in vitro studies in § 320.63, but not in § 320.32 of the interim rule, FDA included the two new sections such that they would conform to the then existing structure of 21 CFR part 320. Former subpart B of part 320 addressed procedures for determining the in vivo bioavailability of drug products whereas former subpart C of part 320 addressed bioequivalence requirements, which may be an in vivo or an in vitro test. Section 505(j) of the Federal Food, Drug and Cosmetic Act (the act) (21 U.S.C. 355(j)) requires that an ANDA include information to show that the drug product for which the applicant is seeking approval is bioequivalent to the approved drug product upon which the applicant relies in seeking approval of its abbreviated application.

Bioequivalence may be demonstrated by in vivo or in vitro bioequivalence methods as determined by the agency. Thus, the reference to an in vitro study in § 320.63 was necessary to accommodate ANDA's submitted under section 505(j) of the act. Because the rule applies to bioavailability and bioequivalence studies required for approval of an

NDA and an ANDA, § 320.63 has been revised to delete the wording “or submitted in support of the approval of.” Section 320.63 also has been revised to remove the reference to a full application which is covered by § 320.38.

Section 320.31 exempts from the requirements of part 312 many bioequivalence and bioavailability studies. The interim rule added as a condition for such an exemption that the sponsor, or any contract research organization to whom the sponsor delegates responsibility to conduct a bioequivalence or bioavailability study, retain reserve samples of the test article and reference standard and release them upon request to FDA (55 FR 47034 at 47036 and 47038). In finalizing the new subpart B structure of 21 CFR part 320, FDA inadvertently omitted this provision. Therefore, FDA has revised § 320.31 to retain the requirements set forth in the interim rule and to clarify the in vivo bioavailability studies from which reserve samples are to be retained.

2. One comment requested that the regulations at §§ 314.125(b)(17) and 320.63 be revised to clarify that the regulations apply only to a pivotal bioequivalence study. The comment also asserted that § 320.32 (§ 320.38 in this final rule) be deleted because a “pivotal” bioavailability study is technically a bioequivalence study and retention of samples from this study is discussed in § 320.63.

The agency agrees with the comment regarding § 314.125(b)(17) and has revised the final rule accordingly. The agency’s conclusions on the types of bioavailability and bioequivalence studies for which the requirements apply and its revisions to §§ 320.38 and 320.63 are discussed in section II.A.1.

3. One comment suggested that, in the case of multiple “biostudies” usually conducted in sequence for a single NDA or ANDA (i.e., a sustained release product) using the same lot of a product, the regulations specify that one supply of retention samples be provided to the testing facility in sufficient quantity for all studies. The comment also asked whether, if additional supplies of the product are needed, the full amount of retention samples also must be supplied again.

FDA believes that the comment misunderstood the interim rule with respect to how the reserve sample is obtained by a contract testing facility. If bioavailability or bioequivalence testing is performed under contract, the study sponsor provides the testing facility with a supply of the test article and of the reference standard sufficient for the testing facility to conduct the study or studies and to remove a portion of the test article and of the reference standard for retention as reserve samples. FDA did not intend that the study sponsor separate out the reserve samples of the test article and reference standard prior to sending the batches to the testing facility. This is to ensure that the reserve samples in fact are representative of the same batches provided by the study sponsor for the testing.

The study sponsor should provide to the testing facility batches of the test product and of the reference standard packaged such that the reserve samples can be randomly selected to ensure that they are in fact representative of the batches provided by the study sponsor and that they are retained in the study sponsor’s original container. Because a study sponsor may provide a testing facility with a variety of container sizes and packaging, FDA intends to be flexible in applying the representativeness requirement. For example, the following random sampling techniques should be used by the testing facility for the container size and packaging described:

a. If a single container of the test article and of the reference standard is provided to the testing facility, the testing facility should remove a quantity of the test article and

of the reference standard from their respective container sufficient to conduct the study; the remainder of each container would be retained as the reserve sample in the original container.

b. If multiple containers of the test article and of the reference standard are provided to the testing facility, the testing facility should randomly select enough containers of the test article and of the reference standard to conduct the study; the remaining containers of the test article and of the reference standard would be retained as the reserve sample in the original containers.

c. If the test article and reference standard are provided to the testing facility in unit dose packaging, the testing facility should randomly select a quantity of unit doses of the test article and of the reference standard sufficient to conduct the study; the remaining unit doses of the test article and of the reference standard would be retained as the reserve samples in the original unit dose packaging. Providing the test article and reference standard in unit dose packaging for conducting the study and in bulk containers for all of the reserve samples would not be acceptable because it prevents the testing facility from randomly selecting the reserve samples. However, as an alternative for the reserve samples, the study sponsor may provide the testing facility with a quantity of unit doses of the test article and of the reference standard equal to at least 24 dose units and the remaining quantity sufficient to retain the “five times quantity” in bulk containers.

d. If the study is to be blinded and the test article and reference standard are provided to the testing facility in unit dose packaging, with each unit dose labeled with a randomization code, the study sponsor must provide the testing facility with a labeled set of the test article and reference standard sufficient to conduct the study and with additional, identically labeled sets sufficient to retain the “five times quantity.” The testing facility should randomly select a labeled set to conduct the study; the remaining labeled sets would be retained in their unit dose packaging as the reserve samples. For a blinded study, the study sponsor should also provide to the testing facility a sealed code for use by FDA should it be necessary to break the code.

If the same batches of the test article and of the reference standard initially provided to the testing facility are used in performing more than one study, only one reserve sample of the test article and reference standard in sufficient quantity need be retained. The reserve samples must be identified as having come from the same batches as used in each specific study. However, if additional supplies of the test article and of the reference standard are needed by a testing facility for performing additional studies, the testing facility must retain the required reserve samples from the subsequent shipment regardless of whether the shipment is from the same batch as that previously provided to the testing facility. This is to ensure that the reserve samples are, in fact, representative of the batch provided by the study sponsor to the testing facility.

4. One comment stated that FDA may request additional “biostudies” after submission of an ANDA and a firm may want to use the same lot of test and reference products as was used in conducting the original study. The comment argued that under the strict retention sample requirement, the firm could not conduct these biostudies without depletion of the retention samples.

In the situation described by the comment, the study sponsor would need to use a different batch of the test and reference products to conduct additional studies if supplies of the batches used to conduct the original studies are depleted. The regulations do not

permit a study sponsor or contract research organization to use its reserve samples to conduct the additional studies.

5. Several comments requested clarification of the regulations about who is responsible for reserve sample retention. One comment argued that the logical responsible party for long-term retention of samples should be the applicant because the applicant is responsible for the manufacture, packaging, testing, and release of the sample of the test article and minimally the packaging, identification testing, and release of the reference standard. The comment stated that it is not practical to sufficiently control the conditions of storage, sample stability, and sample retention at a contract facility after the completion of a study. One comment argued that some outside testing facilities such as universities, hospitals, and clinics do not have the space or proper environment to hold the reserve samples at all or to hold them at the study location, and many do not have the authority to hold certain reserve samples such as controlled substances. Another comment suggested that the regulations provide for the use of independent, third party organizations for the storage of reserve samples. Still another comment stated that the applicant should have the option of storing reserve samples at a company facility rather than at a contract laboratory.

The agency reaffirms that reserve sample retention is the responsibility of the entity performing the bioavailability or bioequivalence study. If the study sponsor performs the study, it is responsible for reserve sample retention for that study; if a study is performed under contract, the contract research organization retains the reserve samples. The purpose of this requirement is to eliminate the possibility for sample substitution by the study sponsor or to preclude a study sponsor from altering a reserve sample from a study conducted by a contract research organization prior to release of the reserve sample to FDA. In several instances, FDA has found that a study sponsor provided the contract testing facility with disguised innovators' products rather than its own proposed product as the test product in certain bioequivalence studies. The reserve samples collected by FDA must have come from the batches provided by the study sponsor to the testing facility for performing a bioavailability or bioequivalence study.

The agency advises that a contract research organization may contract with an independent, third party to provide storage for reserve samples if the contract research organization does not have facilities to store the samples under conditions consistent with product labeling. In this situation, the contract research organization shall provide to the study sponsor, for submission in the bioavailability or bioequivalence study data, the name and address of the facility at which the reserve samples will be stored. A new paragraph (h) is added to §320.38 to include this provision. The agency notes that hospitals and clinics may wish to consider using their pharmacies for storage of the reserve samples.

With respect to retention of reserve samples that are controlled substances, the burden is on the person who is responsible for retaining the samples to comply with all applicable requirements of the Controlled Substances Act (21 U.S.C. 801) and its implementing regulations.

6. One comment asked who had responsibility for reserve sample retention when a contract research organization administers the drug and collects biological samples, but the biological samples are then returned to the applicant for analysis.

For purposes of this regulation, the agency would consider the contract research organization to have conducted the study and to be responsible for retaining the reserve

samples. Similarly, if one contract research organization administers the drug and another contract research organization performs an analysis of the biological samples, the contract research organization that administers the drug would retain the reserve samples.

B. Reserve Sample Retention Period

7. Numerous comments addressed the length of the sample retention period. The interim rule requires that reserve samples be retained for a period of at least 5 years following the date on which the application or supplemental application is approved, or, if such application or supplemental application is not approved, at least 5 years following the date of completion of a bioavailability or bioequivalence study. The interim rule specifically requested comment on the appropriateness of the retention period.

Most of the comments expressed concern that most reserve samples would not exhibit the stability necessary to maintain strength, quality, and purity over such a prolonged period of time, and, therefore, there could be no guarantee that the samples would be appropriate for evaluation by FDA as intended by the interim rule. Requiring special storage conditions, e.g., refrigeration or dehumidification, to prolong a product's stability beyond its normal shelf life would result in a significant expenditure to the applicant or contract research organization responsible for sample retention. Some comments noted that the 5-year period only begins when the application is approved and, in terms of real time, this could be 6 to 8 years for a generic drug product and 7 to 12 years for a new chemical entity. One comment suggested 3 years rather than 5 years as an appropriate retention period; another comment suggested 2 years past submission of an application or supplement, or until the application is approved, whichever occurs first. One comment suggested that FDA make the sample retention period consistent with the good laboratory practice regulations in 21 CFR 58.195(b) and (c). Another comment suggested a retention period of 5 years from the date the bioavailability or bioequivalence study was completed arguing that NDA and ANDA approval dates are not routinely communicated to a contract testing facility due to potential conflicts of interest.

The 5-year reserve sample retention period is intended to permit flexibility by FDA in its collection and testing of retention samples. Ordinarily, the reserve samples, or a portion of the reserve samples, will be collected by FDA personnel directly from the study sponsor or contract research organization at the storage site during a preapproval inspection. FDA's priorities for preapproval inspection and sample collection include narrow therapeutic range drugs, new chemical entities, and generic versions of the 200 most prescribed drugs. For drug products not represented in one of these priority categories, a preapproval inspection would be triggered when the applicant's manufacturing facility is new or has not been recently inspected, and when the NDA or ANDA is the initial application for the applicant. In those cases where preapproval inspections were not conducted and reserve samples were not collected prior to approval of an application or abbreviated application, retention of the reserve samples for the 5-year period would permit their availability for collection and testing after approval. Thus, any retention period that would not continue beyond the approval date of an application, as suggested by some comments, would be unacceptable because it would not provide for the availability of the samples in those situations where a preapproval inspection and sample collection were not conducted or where questions arose after approval about a study sponsor's bioequivalence or bioavailability data.

The agency recognizes that a product retained beyond its normal shelf life may not exhibit the stability necessary to maintain its identity, strength, quality, and purity. However, certain types of analyses can be performed on a product to determine that the test article was indeed used in performing a bioavailability or bioequivalence study and that there was no substitution of the reference standard for the test article. Generally, the formulation of the test article and reference standard will differ. For example, different excipients such as binders, fillers, and lubricants may be used; and products may contain tracer ingredients that are unique to the identification of a particular product. Appropriate analyses can be performed on a product retained beyond its expiration date to detect these differences.

8. One comment asked that FDA clarify in the rule that the retention samples may be kept in any appropriate container and need not necessarily duplicate the containers for the products used in the “biostudy.” The comment stated that, in many studies, the drug supplied is packaged in individual unit doses or small bottles containing a single day’s supply for each study participant. In such cases, if 500 doses are needed for the retention sample, an appropriately packaged bottle of 500 should be allowed, i.e., not 500 unit doses. Another comment recommended that solution dosage forms, parenterals, inhalation aerosols, biologicals, and other specialized delivery devices where storage, stability, and security could be problematic be excluded from retention status.

FDA does not agree that retention samples be kept in any appropriate container. The reserve samples should be retained in the same container/closure system in which the study sponsor provides to the testing facility the supplies of the test article and reference standard. This will provide to FDA evidence as to how the supplies of the test article and reference standard were received by the testing facility. As noted in section II.A.3, the study sponsor should provide to the testing facility supplies of the test article and of the reference standard packaged such that the reserve samples can be randomly selected by the testing facility and retained in the study sponsor’s container/closure system.

The agency disagrees with the comment suggesting that certain dosage forms be excluded from the reserve sample retention requirement. The agency must have adequate assurance that the bioavailability and bioequivalence results upon which FDA bases approval of an application are reliable. Therefore, reserve samples of all products used to conduct the types of bioavailability or bioequivalence studies described in this rule must be available for later examination/analysis by FDA.

9. One comment suggested that reserve samples be stored according to the approved labeling and that this be clarified in the rule. Another comment stated that, for new development compounds, appropriate storage information is not always available during the early stages of development, or if it is, such storage conditions are usually limited or restricted. In such a case, storage is usually in accordance with the sponsor’s storage requirements.

The agency did not intend that special storage conditions be provided to prolong a product’s stability beyond its normal shelf life. All reserve samples are to be retained and stored under conditions consistent with product labeling. The agency believes that, for the types of bioavailability and bioequivalence studies described above for which reserve samples are to be retained, appropriate storage information will be available in the product’s labeling. Section 320.38(e) of this final rule (§ 320.32(c) of the interim rule) has been revised to require storage under conditions consistent with product labeling.

10. One comment argued that, for a contract research organization, determining the starting date for sample retention is often a problem because the contract research organization does not have direct knowledge or control over such events as discontinuance of a compound's development, submission of an application for approval, or approval of an application for marketing, which initiates the 5-year retention period.

The agency believes that a contract research organization can make arrangements with a study sponsor regarding notification of the status of the application for which a bioavailability or bioequivalence study has been conducted, and that it is the responsibility of the contract research organization to obtain such information in order to comply with the sample retention requirements of this rule. There is nothing in the regulations that prevents the inclusion, in the contract between a study sponsor and a contract research organization, of a condition requiring the study sponsor to notify the contract research organization of those regulatory actions about a test article that are necessary for a contract research organization to comply with this rule, e.g., discontinuance of the development of a drug, submission of an application for approval, or date of approval of an application for the test article. Thus, the agency recommends that all contract research organizations insist on the inclusion of such a condition in their contract with the study sponsor.

11. One comment stated that the reference standard used for determining bioavailability is usually a solution or suspension that is made up especially for the study, which would rarely be expected to be stable for more than 6 years. The comment suggested an exemption from the sample retention requirements for these reference standards.

As discussed under section II.A.1.a.(i), a reserve sample of the reference standard from the batch used to conduct a bioavailability study comparing the test product to a reference oral solution, suspension, or injection need not be retained. If the study needs to be repeated, the reference standard would be prepared at the time of the study.

12. One comment asked if the 5-year sample retention requirement would apply if, after receiving a not approvable letter from the agency, the applicant decides to withdraw the NDA.

The final rule, like the interim rule, requires that if an application or supplemental application is not approved, reserve samples be retained at least 5 years following the date of completion of the bioavailability or bioequivalence study in which the sample, from which the reserve sample was obtained, was used. A decision by the applicant to withdraw its application in response to a not approvable letter is without prejudice to refile. Therefore, because an applicant may resubmit its application, data from previously conducted bioavailability studies could be used for approval of the resubmitted application. Thus, in the situation described by the comment, the reserve samples must be retained for the required time period. The agency believes, however, that in some cases, given the time that may elapse between the conduct of a study and the completion of FDA's review of an application, the 5-year period following the date of completion of a bioavailability study will have expired.

13. One comment asked if the agency would grant a waiver reducing the reserve sample amounts if sufficient quantities of a drug product were not available due to production restrictions such as high product costs or high potency compounds.

The agency does not intend to grant waivers from the requirements of this rule. FDA must be assured that the bioavailability and bioequivalence results upon which FDA bases approval are reliable. Therefore, samples of the products used to conduct the types

of bioavailability and bioequivalence studies described in this rule must be available for FDA's analysis. An applicant should consider the requirements of this rule in determining its production quantities.

C. Quantity of Reserve Samples

14. The interim rule required that a sufficient quantity of the reserve samples be retained to permit FDA to perform five times all of the release tests required in the application or supplemental application.

Several comments argued that the quantity of both the test article and reference standard seemed excessive, and asked the agency to reconsider the retention sample size requirement in light of the intended uses for the retained samples. Some comments suggested that the regulations be modified to reflect either the requirement of twice the quantity needed for release testing under the current good manufacturing practice (CGMP) regulations, or the NDA methods validation requirement in 21 CFR 314.50(e) of three times the quantity necessary to perform each test. Two comments argued that samples of the reference standard usually are obtained from the marketplace, and it can be extremely difficult to find in large quantities a single lot of a product sufficient to conduct the study and to retain a portion for the reserve sample. One of the comments suggested retention of two intact bottles of the reference standard sample for identification of lot number, expiry, strength, etc., for 3 years.

One comment asserted that acquiring large quantities of material, if available, for no purpose other than satisfying an excessive retention requirement is an unnecessary economic cost. In addition, the comment suggested that, in assessing potential uses, the agency consider that: (1) the materials to be tested may have been well into their anticipated shelf life at the time of the bioavailability or bioequivalence testing, and (2) the materials will inevitably continue to deteriorate over time such that many potential tests of the retained material (e.g., rerun of release tests or of the "biostudy" itself) could well be meaningless even if those retests are conducted during the application review process. Another comment asserted that the regulation will cause an economic impact in that additional storage space will need to be obtained and existing space modified in order to meet unique and long-term storage requirements. One comment stated that it may not be practical to retain the five times quantity for special dosage forms in limited supply such as early development lots for bioavailability studies.

FDA's experience in the testing of reserve samples of drug products used in a bioavailability or bioequivalence study is that the five times quantity required for the test article and the reference standard is needed to perform necessary testing. Although the interim rule required a "sufficient quantity to permit FDA to perform five times all of the release tests required in the application or supplemental application," FDA does not intend to perform release tests on the reserve samples. The five times quantity standard is intended to provide a yardstick for the retention of a sufficient quantity of the samples by all study sponsors and contract research organizations. The reserve samples of the test article and of the reference standard are used by FDA to conduct a chemical and physical examination of the samples to assure the identity and composition of the test article and reference standard. This is necessary to detect fraudulent substitution of the reference standard for the test article in conducting a bioavailability or bioequivalence study. Although generic drugs are expected to be functionally equivalent to their brand-name coun-

terparts, they are not expected to be identical in all physical and chemical aspects because of differences in, for example, identity and proportions of excipients. These differences are used by FDA to determine if fraudulent substitution has occurred. Any remaining reserve sample is held by FDA in the event that additional testing is necessary. For example, FDA may need to repeat the bioavailability or bioequivalence testing or to perform other appropriate analyses such as content uniformity and dissolution testing on the samples.

The agency agrees that, for some reference standards, only limited quantities may be available in the marketplace. However, FDA believe that sufficient quantities are available to conduct the necessary “biostudies” to provide the required reserve samples.

The agency continues to believe that the five times quantity standard is an appropriate standard for the reserve sample of the test article and of the reference standard and is retaining that standard in this final rule. However, study sponsor or contract research organization may consult with the agency if it believes certain dosage forms present unreasonable storage problems. If a contract research organization is unsure of what quantity constitutes the five times quantity, it should contact the study sponsor.

15. One comment asked if the requirement to retain a sufficient quantity of reserve sample to allow FDA to perform five times all of the release tests required in the application or supplemental application provides enough sample for FDA to repeat the bioavailability or bioequivalence testing or perform other appropriate testing, if necessary. Another comment asked if the required retention sample size included sufficient material to allow a so-called “split” sample so that the applicant could independently verify any tests conducted by the agency or the retained material.

The quantity of sample required to be retained is sufficient for all testing by FDA including a repeat of a bioavailability or bioequivalence study if necessary. No additional samples beyond the five times quantity need be retained by the study sponsor or contract research organization. However, the required retention sample size does not provide sufficient material for independent testing by the study sponsor.

16. One comment asked for clarification of the sample retention requirement with respect to products that are manufactured in a dry form and need to be reconstituted just prior to use in a study.

For purposes of the sample retention requirement in this rule, the reserve sample would consist of the product in the dry form, not the reconstituted form.

17. Two comments requested clarification of the effective date of the interim rule with respect to ongoing studies. One comment argued that testing programs already underway as of November 8, 1990, the effective date of the interim rule, should not have to be restarted because insufficient material is available to satisfy the sample retention requirement in addition to that necessary to conduct the required tests. The comment further stated that even if additional material from the same product lots were available, it could not be “representative” of the material submitted for the “biostudies” unless it had been submitted to the testing laboratory at the same time as the original material. One comment argued that, at a minimum, the new requirements should be deemed to be satisfied, in the case of ongoing studies, by the retention of as much material as is available after the testing is complete. This would also apply to study programs which commenced prior to November 8, 1990, if subsequent studies were planned to use the same limited lots of test or reference drugs.

The requirements established in the interim rule apply only to bioavailability and bioequivalence studies that were initiated on or after November 8, 1990.

18. One comment addressed the provisions of §§ 314.125(b)(17) and 314.150(b)(9), which state that FDA may refuse to approve, or to withdraw approval of, an application if an applicant or contract research organization refuses to permit an inspection of its facilities or records, or refuses to submit to FDA reserve samples when requested. The comment asked that when a contract research organization, without the knowledge or approval of the applicant, refuses to permit an FDA inspection of facilities or records relevant to a study or to submit to FDA reserve samples of drug products used in the study, the rule provide for notification to the applicant with an opportunity to intervene before any agency action to refuse to approve, or to withdraw the approval of, an application.

The agency advises that the regulations concerning FDA's action to refuse to approve an application or to withdraw the approval of an application are set forth under §§ 314.120 and 314.150, respectively. Thus, an applicant will have an opportunity to respond to any agency action by the procedures for denying or withdrawing the approval of an application. The agency emphasizes that, because actions or inactions of a contract research organization may affect the status of an applicant's application, the applicant may well wish to assure that the obligation to permit inspection and to release or submit to FDA reserve samples is included in any contract.

19. One comment suggested that the written assurance that the reserve samples came from the same samples as used in the specific bioavailability or bioequivalence study required under § 320.32(e) of the interim rule be modeled after 21 CFR 10.20(i), which requires that submissions to the Dockets Management Branch include a statement that, to the best of the knowledge, information, and belief of the person making the submission, the statements made in the submission are true and accurate. The comment argued that due to the extended period of time that samples must be retained and potential personnel turnover during that time, the person executing the written assurance may not have first-hand knowledge of the history of the sample being released to the agency, and may have to rely on company documentation. The comment further argued that an assurance provided under the interim rule would subject an individual to potential criminal liability under 18 U.S.C. 1001, based upon whether the statement is true or not, even though the person may not have direct personal knowledge of its falsity. Another comment asked in what form the written assurance should be. One comment asserted that both the sponsor and testing laboratory should certify that the reserve samples are those used in the specific bioavailability or bioequivalence studies submitted to FDA, and that copies of the certification statements should be held by both parties and be made available to FDA upon request.

The agency agrees that the person executing the written assurance may not have firsthand knowledge of the history of the samples and may have to rely on records of the applicant or contract research organization. Therefore, FDA has revised § 320.38(g) (§ 320.32(e) in the interim rule) to require that the applicant or contract research organization provide a written assurance that, to the best knowledge and belief of the individual executing the assurance, the reserve samples came from the same samples as used in the specific bioavailability or bioequivalence study identified by the agency. The written assurance may be in the form of a certification or other appropriate form. Because it is

the contract research organization that separates out the reserve samples from the supplies of the test article and reference standard provided by the study sponsor rather than the study sponsor, FDA does not believe that the study sponsor can assure that the reserve samples came from the same batch as used in a specific bioavailability or bioequivalence study. Therefore, FDA does not agree with the assertion that both the study sponsor and testing laboratory certify with respect to the reserve sample.

20. Two comments asked that the requirement in § 320.32(b) of the interim rule, which requires that samples be positively identified as having come from the same sample as used in the specific bioavailability or bioequivalence study, be more specific as to what is expected.

The agency believes that specific ways to identify reserve samples and the study in which they were used should be left to the study sponsor or contract research organization responsible for retaining the samples. Therefore, the agency declines to provide specificity in the regulation. Appropriate identification may, however, consist of but not be limited to, including on the sample container and in the study report, the product name, lot number, and study number.

21. One comment suggested that for inhalants that require exhaustive number of dosage units to be tested for release and require large storage space, a definitive number of retention samples, for example, 10 to 20 units, should be sufficient.

As discussed in section II.C.14, FDA does not intend to perform release testing on the reserve samples. Nevertheless, the agency does not agree that 10 to 20 units of an inhalant dosage form are sufficient for FDA's analysis and testing. As also discussed in section II.C.14, the reserve samples ordinarily will be used by FDA to perform a chemical and physical examination of the samples. The agency may also need to perform analyses such as content uniformity and dissolution for solid oral dosage forms and may need to repeat the bioavailability or bioequivalence testing. The agency concludes that the quantity of the reserve sample of an inhalant test article and of the reference standard needed for testing and analyses must be at least 50 units.

D. Need for Additional Requirements

22. In the preamble to the interim rule, FDA stated it was considering whether additional requirements were necessary to ensure the integrity of the reserve samples and invited comment on questions relating to storage area, need for a sample custodian, and packaging of the reserve samples. Seventeen comments responded to the agency's questions or otherwise addressed the issue of the need for additional requirements.

Two comments recommended that, under CGMP regulations, applicants be required to adopt written procedures for selection of samples from drug lots used in bioavailability or bioequivalence testing and for secure transmission of these samples to internal facilities or contract research organizations for "biotesting" and storage. Additional written procedures should establish the security measures to be followed for retained samples, including requirements for the storage area, sample custodian, and packaging of the samples to ensure that sample integrity is not compromised. Most of the comments recommended that the reserve samples be stored in an area where access is controlled and that is separate from the testing area. One comment, however, asked for a clarification of the wording "separate from" arguing that it is not necessary to require separation from the testing area so long as the storage area is segregated and access is controlled. A majority of the

comments suggested that the need for a sample custodian should be left up to the applicant or testing facility and not be required by regulation. Responses to the questions of how the reserve samples should be packaged during the retention period to ensure that sample integrity is not compromised and to prevent tampering varied among the responders. Some comments recommended that the packaging of the reserve samples be in the same container/closure as that provided to the testing facility or a normal marketed package; other comments suggested using tamper-resistant packaging, using a sealed protective container such as glass, taking appropriate measures to prevent tampering, or that there is no need for specific packaging requirements if there is appropriate documentation based on written operating procedures.

FDA agrees with those comments recommending that reserve samples be stored in an area separate from the testing area and with controlled access. Accordingly, § 320.38(e) (§ 320.32(c) in the interim rule) has been revised to require that each reserve sample be stored in an area segregated from the area where testing is conducted and with access limited to authorized personnel. The agency has used the phrase “segregated from” rather than “separate from” because it is not intended that the storage area necessarily be in a different room, building, or facility. The requirement is intended to ensure that enough physical separation be employed by the study sponsor or contract research organization as is necessary to ensure that the integrity of the reserve sample is not compromised during the retention period.

The agency is not including other additional requirements at this time. If, based on FDA’s inspectional experience and collection of reserve samples, the agency believes additional requirements are needed to ensure the integrity of the samples, it will propose appropriate revisions to this rule. The rule does not preclude study sponsors from adopting written procedures for the selection and transmission to the testing facility or contract research organization of the test article and reference standard for testing and storage of the reserve samples.

E. Other Comments

23. One comment noted that the interim rule did not address the situation where a contract testing laboratory goes out of business or is otherwise not in a position to continue to meet its obligations under the rule. The comment suggested that, under such circumstances, the sponsor should be allowed to recover from the contractor any retained samples from the studies it sponsored because sponsors are already required under the interim rule to maintain samples for studies conducted in-house. This would obviate the need for special procedures to deal with the insolvency of contractors or other potential problems with third party custodians, and would greatly simplify FDA’s ability to obtain the samples because they would be readily available from the sponsor even for studies conducted by contract testing laboratories in foreign countries.

The agency agrees that the rule should provide for the transfer of reserve samples if a contract research organization goes out of business, but does not agree that the samples should be transferred to the sponsor or applicant for whom the contract research organization conducted the bioavailability or bioequivalence study. Rather, to preclude the possibility for sample substitution by a study sponsor or to preclude a study sponsor from altering a reserve sample, FDA concludes that the reserve samples should be transferred to an appropriate, independent third party, e.g., a commercial storage facility or a university.

Therefore, a new paragraph (i) is added to § 320.38 (§ 320.32 in the interim rule), which states that when a contract research organization conducting a bioavailability or bioequivalence study requiring reserve sample retention goes out of business, it shall transfer its reserve samples to an appropriate, independent third party and shall notify in writing the sponsor of the study and provide the sponsor with the name and address of the facility to which the reserve samples have been transferred. Because the comment did not describe the circumstances in which a contract research organization “is otherwise not in a position to continue to meet its obligations under the rule,” no further revision of the rule has been made.

24. One comment suggested that after the retention period is up, samples should be returned to the sponsor for proper accountability and destruction as required under CGMP’s.

The agency advises that this final rule, like the interim rule, does not preclude such an approach. The study sponsor may wish to include in the contractual agreement with the contract research organization provisions for handling of the reserve samples after the retention period has expired. It should be noted, however, that the CGMP regulations do not address disposition of outdated reserve samples required to be retained under those regulations.

25. One comment suggested using a standardized photographic archiving procedure to show the drug product at the time of dosing for the bioavailability or bioequivalence study. This photographic record could be retained beyond the expiration date of the product, and would demonstrate the product’s physical appearance.

The agency does not intend to require a photographic archiving procedure in this final rule; however, this does not preclude a testing facility from adopting such a procedure. FDA intends, as part of its physical analysis of a product that is a solid oral dosage form, to photograph each strength of each product to clearly document its shape, color, and distinctive markings. These photographs will be retained by FDA for later use in comparing subsequent batches of the test article or in comparing the test article to the reference standard.

26. Several comments addressed a statement in the preamble to the interim rule that states “in vitro and animal in vivo bioequivalence and bioavailability studies are within the scope of the good laboratory practice regulations.” The comments argued that animal bioequivalence and bioavailability studies have not previously been considered within the scope of 21 CFR part 58 except when conducted as part of a toxicology protocol or when conducted to directly support a toxicology protocol. The comments asked that FDA further clarify the scope of the preamble statement and this rule.

The agency believes the regulations at 21 CFR part 58 are ambiguous with respect to in vitro and animal in vivo bioavailability and bioequivalence studies required for approval of an NDA or ANDA; however, it is understood that no one considers those regulations to apply to the types of studies subject to this rule. Therefore, the requirements of this rule do not affect the reserve sample retention requirements under 21 CFR part 58.

III. Economic Impact

FDA has examined the economic consequences of the changes implemented by the final rule in accordance with Executive Order 12291 and the Regulatory Flexibility Act

(Pub. L. 96–354). This final rule more clearly defines the types of in vivo bioavailability studies for which reserve samples are to be retained. Although this rule has been in place as an interim regulation, the agency is not aware that it has imposed any undue costs. Nevertheless, because several comments to the record alluded to potential costs, the agency has conducted a Threshold Assessment of the final rule, which is on file with the Dockets Management Branch (HFA–305), rm. 1–23, 12420 Parklawn Dr., Rockville, MD 20657.

The agency's assessment presents costs of retaining samples for an estimated 360 marketing applications per year. The study addresses both the additional storage costs and the acquisition costs of the test articles and reference standards. Storage costs were estimated on the basis of each sample requiring 0.5 square feet of storage for 5 years, and amounted to about \$2,800. These costs would be roughly proportionate to the duration of the retention period. Acquisition costs of about \$94,000 for reference samples were obtained from a survey of average retail prices of 16 well-prescribed medicines. Although individual circumstances may arise where storage or acquisition costs for a particular sample could rise substantially above these estimates, the agency believes that, on average, the annual costs of this rule will be about \$100,000. FDA believes that these costs will likely be more than offset by the societal benefits of this rule, i.e., the added assurance that FDA's drug approval process functions effectively to ensure that only safe and effective drug products enter the marketplace. Accordingly, the agency concludes that this final rule is not a major rule as defined by Executive Order 12291, and certifies that the final rule will not have a significant impact on a substantial number of small entities, as defined by the Regulatory Flexibility Act.

Notwithstanding the above agency assessment, FDA believes that it would be desirable to have available specific data with respect to various sample retention periods and quantities of samples to be retained. Therefore, the agency is soliciting information on the following areas:

(1) The incremental costs of retention of samples for 3 years relative to 4 years, and 4 years relative to 5 years;

(2) The incremental costs of retention of a "4 times quantity" of samples relative to a "5 times quantity"; and

(3) Any information on the incremental benefits of either retaining greater quantities of samples, or of retaining samples for greater periods of time.

Interested persons may, on or before May 28, 1993 submit to the Dockets Management Branch (address above) information on these areas. Two copies of any information should be submitted, except that individuals may submit one copy. Information submitted is to be identified with the docket number found in brackets in the heading of this document. Information received may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

IV. Environmental Impact

The agency has determined under 21 CFR 25.24(a)(8) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

List of Subjects

21 CFR Part 312

Drugs, Exports, Imports, Investigations, Labeling, Medical research, Reporting and recordkeeping requirements, Safety.

21 CFR Part 314

Administrative practice and procedure, Confidential business information, Drugs, Reporting and recordkeeping requirements.

21 CFR Part 320

Drugs, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, and authority delegated to the Commissioner of Food and Drugs, 21 CFR parts 312, 314, and 320 are amended as follows:

PART 312—INVESTIGATIONAL NEW DRUG APPLICATION

1. The authority citation for 21 CFR part 312 continues to read as follows:

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 701 of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 371); sec. 351 of the Public Health Service Act (42 U.S.C. 262).

2. Section 312.57 is amended by revising paragraph (c) to read as follows:

§ 312.57 Recordkeeping and record retention.

* * * * *

(c) A sponsor shall retain reserve samples of any test article and reference standard identified in, and used in any of the bioequivalence or bioavailability studies described in, § 320.38 or § 320.63 of this chapter, and release the reserve samples to FDA upon request, in accordance with, and for the period specified in § 320.38.

* * * * *

PART 314—APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG OR AN ANTIBIOTIC DRUG

3. The authority citation for 21 CFR part 314 continues to read as follows:

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 701, 706 of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 371, 376).

4. Section 314.125 is amended by revising paragraph (b)(17) to read as follows:

§ 314.125 Refusal to approve an application or abbreviated antibiotic application.

* * * * *

(b)* * *

(17) The applicant or contract research organization that conducted a bioavailability or bioequivalence study described in § 320.38 or § 320.63 of this chapter that is contained in the application or abbreviated antibiotic application refuses to permit an inspection of facilities or records relevant to the study by a properly authorized officer or employee

of the Department of Health and Human Services or refuses to submit reserve samples of the drug products used in the study when requested by FDA.

* * * * *

5. Section 314.127 is amended by revising paragraph (b) to read as follows:

§ 314.127 Refusal to approve an abbreviated new drug application.

* * * * *

(b) FDA may refuse to approve an abbreviated application for a new drug if the applicant or contract research organization that conducted a bioavailability or bioequivalence study described in § 320.63 of this chapter that is contained in the abbreviated new drug application refuses to permit an inspection of facilities or records relevant to the study by a properly authorized officer or employee of the Department of Health and Human Services or refuses to submit reserve samples of the drug products used in the study when requested by FDA.

6. Section 314.150 is amended by revising paragraph (b)(9) to read as follows:

§ 314.150 Withdrawal of approval of an application or abbreviated application.

* * * * *

(b)* * *

(9) That the applicant or contract research organization that conducted a bioavailability or bioequivalence study described in § 320.38 or § 320.63 of this chapter that is contained in the application or abbreviated application refuses to permit an inspection of facilities or records relevant to the study by a properly authorized officer or employee of the Department of Health and Human Services or refuses to submit reserve samples of the drug products used in the study when requested by FDA.

* * * * *

PART 320—BIOAVAILABILITY AND BIOEQUIVALENCE REQUIREMENTS

7. The authority citation for 21 CFR part 320 continues to read as follows:

Authority: Secs. 201, 501, 502, 505, 507, 701 of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 321, 351, 352, 355, 357, 371).

8. Section 320.31 is amended by revising paragraph (c), by adding new paragraph (d), and by removing paragraph (e) and (f) to read as follows:

§ 320.31 Applicability of requirements regarding an “Investigational New Drug Application.”

* * * * *

(c) The provisions of parts 50, 56, and 312 of this chapter are applicable to any bioavailability or bioequivalence study in humans conducted under an IND.

(d) A bioavailability or bioequivalence study in humans other than one described in paragraphs (a) through (c) of this section is exempt from the requirements of part 312 of this chapter if the following conditions are satisfied:

(1) If the study is one described under §320.38(b) or §320.63, the person conducting the study, including any contract research organization, shall retain reserve samples of any test article and reference standard used in the study and release the reserve samples to FDA upon request, in accordance with, and for the period specified in, §320.38; and

(2) An in vivo bioavailability or bioequivalence study in humans shall be conducted in compliance with the requirements for institutional review set forth in part 56 of this chapter, and informed consent set forth in part 50 of this chapter.

9. Section 320.38 is revised to read as follows:

§ 320.38 Retention of bioavailability samples.

(a) The applicant of an application or supplemental application submitted under section 505 or 507 of the Federal Food, Drug and Cosmetic Act, or, if bioavailability testing was performed under contract, the contract research organization shall retain an appropriately identified reserve sample of the drug product for which the applicant is seeking approval (test article) and of the reference standard used to perform an in vivo bioavailability study in accordance with and for the studies described in paragraph (b) of this section that is representative of each sample of the test article and reference standard provided by the applicant for the testing.

(b) Reserve samples shall be retained for the following test articles and reference standards and for the studies described:

(1) If the formulation of the test article is the same as the formulation(s) used in the clinical studies demonstrating substantial evidence of safety and effectiveness for the test article's claimed indications, a reserve sample of the test article used to conduct an in vivo bioavailability study comparing the test article to a reference oral solution, suspension, or injection.

(2) If the formulation of the test article differs from the formulation(s) used in the clinical studies demonstrating substantial evidence of safety and effectiveness for the test article's claimed indications, a reserve sample of the test article and of the reference standard used to conduct an in vivo bioequivalence study comparing the test article to the formulation(s) (reference standard) used in the clinical studies.

(3) For a new formulation, new dosage form, or a new salt or ester of an active drug ingredient or therapeutic moiety that has been approved for marketing, a reserve sample of the test article and of the reference standard used to conduct an in vivo bioequivalence study comparing the test article to a marketed product (reference standard) that contains the same active drug ingredient or therapeutic moiety.

(c) Each reserve sample shall consist of a sufficient quantity to permit FDA to perform five times all of the release tests required in the application or supplemental application.

(d) Each reserve sample shall be adequately identified so that the reserve sample can be positively identified as having come from the same sample as used in the specific bioavailability study.

(e) Each reserve sample shall be stored under conditions consistent with product labeling and in an area segregated from the area where testing is conducted and with access limited to authorized personnel. Each reserve sample shall be retained for a period of at least 5 years following the date on which the application or supplemental application is approved, or, if such application or supplemental application is not approved, at least 5 years following the date of completion of the bioavailability study in which the sample from which the reserve sample was obtained was used.

(f) Authorized FDA personnel will ordinarily collect reserve samples directly from the applicant or contract research organization at the storage site during a preapproval

inspection. If authorized FDA personnel are unable to collect samples, FDA may require the applicant or contract research organization to submit the reserve samples to the place identified in the agency's request. If FDA has not collected or requested delivery of a reserve sample, or if FDA has not collected or requested delivery of any portion of a reserve sample, the applicant or contract research organization shall retain the sample or remaining sample for the 5-year period, specified in paragraph (e) of this section.

(g) Upon release of the reserve samples to FDA, the applicant or contract research organization shall provide a written assurance that, to the best knowledge and belief of the individual executing the assurance, the reserve samples came from the same samples as used in the specific bioavailability or bioequivalence study identified by the agency. The assurance shall be executed by an individual authorized to act for the applicant or contract research organization in releasing the reserve samples to FDA.

(h) A contract research organization may contract with an appropriate, independent third party to provide storage of reserve samples provided that the sponsor of the study has been notified in writing of the name and address of the facility at which the reserve samples will be stored.

(i) If a contract research organization conducting a bioavailability or bioequivalence study that requires reserve sample retention under this section or § 320.63 goes out of business, it shall transfer its reserve samples to an appropriate, independent third party, and shall notify in writing the sponsor of the study of the transfer and provide the study sponsor with the name and address of the facility to which the reserve samples have been transferred.

10. Section 320.63 is revised to read as follows:

§ 320.63 Retention of bioequivalence samples.

The applicant of an abbreviated application or a supplemental application submitted under section 505 or 507 of the Federal Food, Drug and Cosmetic Act, or, if bioequivalence testing was performed under contract, the contract research organization shall retain reserve samples of any test article end reference standard used in conducting an in vivo or in vitro bioequivalence study required for approval of the abbreviated application or supplemental application. The applicant or contract research organization shall retain the reserve samples in accordance with, and for the period specified in, §320.38 and shall release the reserve samples to FDA upon request in accordance with §320.38.

Dated March 3, 1993.

Michael R. Taylor,

Deputy Commissioner for Policy.

[FR Doc. 93-9927 Filed 4-27-93; 8:45 am]

BILLING CODE 4160-01-F

Appendix E

USP24–NF19 Information; Monographs; Tests; Assays

In follow-up to Pages 5 and 6 *supra*, the USP24-NF19 has graciously provided us with the list of general chapters available for citations in any of the 3700 plus monographs, and the titles of all test standards that have been added, revised, or deleted for the latest edition. This should assist the reader in identifying those test standards and monographs in which changes in nomenclature, procedure, or substance have been made.

Guide to General Chapters

(For complete alphabetic list of all general chapters in this Pharmacopeia, see under “General chapters” in the index.)

General Tests and Assays

General Requirements for Tests and Assays

- ⟨1⟩ Injections . . . 1775
- ⟨11⟩ USP Reference Standards . . . 1777

Apparatus for Tests and Assays

- ⟨16⟩ Automated Methods of Analysis . . . 1801
- ⟨21⟩ Thermometers . . . 1808
- ⟨31⟩ Volumetric Apparatus . . . 1808
- ⟨41⟩ Weights and Balances . . . 1809

Microbiological Tests

- ⟨51⟩ Antimicrobial Effectiveness Testing . . . 1809
- ⟨55⟩ Biological Indicators—Resistance Performance Tests . . . 1811
- ⟨61⟩ Microbial Limit Tests . . . 1814
- ⟨71⟩ Sterility Tests . . . 1818

Biological Tests and Assays

- ⟨81⟩ Antibiotics—Microbial Assays . . . 1823
- ⟨85⟩ Bacterial Endotoxins Test . . . 1829
- ⟨87⟩ Biological Reactivity Tests, In Vitro . . . 1831
- ⟨88⟩ Biological Reactivity Tests, In Vivo . . . 1832
- ⟨91⟩ Calcium Pantothenate Assay . . . 1836
- ⟨111⟩ Design and Analysis of Biological Assays . . . 1837
- ⟨115⟩ Dexpanthenol Assay . . . 1847
- ⟨121⟩ Insulin Assays . . . 1848
- ⟨141⟩ Protein—Biological Adequacy Test . . . 1849
- ⟨151⟩ Pyrogen Test . . . 1850
- ⟨161⟩ Transfusion and Infusion Assemblies and Similar Medical Devices . . . 1851
- ⟨171⟩ Vitamin B₁₂ Activity Assay . . . 1851

Chemical Tests and Assays

IDENTIFICATION TESTS

- ⟨181⟩ Identification—Organic Nitrogenous Bases . . . 1853
- ⟨191⟩ Identification Tests—General . . . 1853
- ⟨193⟩ Identification—Tetracyclines . . . 1855
- ⟨197⟩ Spectrophotometric Identification Tests . . . 1855
- ⟨201⟩ Thin-Layer Chromatographic Identification Test . . . 1856

LIMIT TESTS

- ⟨206⟩ Aluminum . . . 1856
- ⟨211⟩ Arsenic . . . 1856
- ⟨221⟩ Chloride and Sulfate . . . 1857
- ⟨223⟩ Dimethylaniline . . . 1858
- ⟨226⟩ 4-Epianhydrotetracycline . . . 1858
- ⟨231⟩ Heavy Metals . . . 1858
- ⟨241⟩ Iron . . . 1860
- ⟨251⟩ Lead . . . 1860

- ⟨261⟩ Mercury . . . 1860
- ⟨271⟩ Readily Carbonizable Substances Test . . . 1862
- ⟨281⟩ Residue on Ignition . . . 1862
- ⟨291⟩ Selenium . . . 1862

OTHER TESTS AND ASSAYS

- ⟨301⟩ Acid-Neutralizing Capacity . . . 1863
- ⟨311⟩ Alginates Assay . . . 1863
- ⟨331⟩ Amphetamine Assay . . . 1864
- ⟨341⟩ Antimicrobial Agents—Content . . . 1864
- ⟨351⟩ Assay for Steroids . . . 1866
- ⟨361⟩ Barbiturate Assay . . . 1866
- ⟨371⟩ Cobalamin Radiotracer Assay . . . 1867
- ⟨381⟩ Elastomeric Closures for Injections . . . 1867
- ⟨391⟩ Epinephrine Assay . . . 1868
- ⟨401⟩ Fats and Fixed Oils . . . 1868
- ⟨411⟩ Folic Acid Assay . . . 1872
- ⟨425⟩ Iodometric Assay—Antibiotics . . . 1872
- ⟨431⟩ Methoxy Determination . . . 1872
- ⟨441⟩ Niacin or Niacinamide Assay . . . 1873
- ⟨451⟩ Nitrite Titration . . . 1875
- ⟨461⟩ Nitrogen Determination . . . 1876
- ⟨466⟩ Ordinary Impurities . . . 1876
- ⟨467⟩ Organic Volatile Impurities . . . 1877
- ⟨471⟩ Oxygen Flask Combustion . . . 1879
- ⟨481⟩ Riboflavin Assay . . . 1879
- ⟨501⟩ Salts of Organic Nitrogenous Bases . . . 1879
- ⟨511⟩ Single-Steroid Assay . . . 1880
- ⟨521⟩ Sulfonamides . . . 1880
- ⟨531⟩ Thiamine Assay . . . 1881
- ⟨541⟩ Titrimetry . . . 1882
- ⟨551⟩ Alpha Tocopherol Assay . . . 1884
- ⟨561⟩ Vegetable Drugs . . . 1884
- ⟨571⟩ Vitamin A Assay . . . 1890
- ⟨581⟩ Vitamin D Assay . . . 1891
- ⟨591⟩ Zinc Determination . . . 1894

Physical Tests and Determinations

- ⟨601⟩ Aerosols . . . 1895
- ⟨611⟩ Alcohol Determination . . . 1912
- ⟨616⟩ Bulk Density and Tapped Density . . . 1913
- ⟨621⟩ Chromatography . . . 1914
- ⟨631⟩ Color and Achromicity . . . 1926

<641> Completeness of Solution . . . 1927
 <643> Total Organic Carbon . . . 1927
 <645> Water Conductivity . . . 1928
 <651> Congealing Temperature . . . 1929
 <661> Containers . . . 1930
 <671> Containers—Permeation . . . 1936
 <691> Cotton . . . 1938
 <695> Crystallinity . . . 1939
 <698> Deliverable Volume . . . 1939
 <699> Density of Solids . . . 1940
 <701> Disintegration . . . 1941
 <711> Dissolution . . . 1941
 <721> Distilling Range . . . 1943
 <724> Drug Release . . . 1944
 <726> Electrophoresis . . . 1951
 <731> Loss on Drying . . . 1954
 <733> Loss on Ignition . . . 1954
 <736> Mass Spectrometry . . . 1954
 <741> Melting Range or Temperature . . . 1958
 <751> Metal Particles in Ophthalmic Ointments . . . 1959
 <755> Minimum Fill . . . 1959
 <761> Nuclear Magnetic Resonance . . . 1959
 <771> Ophthalmic Ointments . . . 1965
 <776> Optical Microscopy . . . 1965
 <781> Optical Rotation . . . 1968
 <785> Osmolarity . . . 1968
 <786> Particle Size Distribution Estimation by Analytical Sieving . . . 1969
 <788> Particulate Matter in Injections . . . 1971
 <791> pH . . . 1977
 <801> Polarography . . . 1978
 <811> Powder Fineness . . . 1981
 <821> Radioactivity . . . 1981
 <823> Radiopharmaceuticals for Positron Emission Tomography—
 Compounding . . . 1988
 <831> Refractive Index . . . 1990
 <841> Specific Gravity . . . 1990
 <846> Specific Surface Area . . . 1990
 <851> Spectrophotometry and Light-Scattering . . . 1992
 <861> Sutures—Diameter . . . 1997
 <871> Sutures—Needle Attachment . . . 1998
 <881> Tensile Strength . . . 1998
 <891> Thermal Analysis . . . 1999
 <905> Uniformity of Dosage Units . . . 2000
 <911> Viscosity . . . 2002

- ⟨921⟩ Water Determination . . . 2003
- ⟨941⟩ X-ray Diffracton . . . 2005

General Information

- ⟨1015⟩ Automated Radiochemical Synthesis Apparatus . . . 2008
- ⟨1035⟩ Biological Indicators . . . 2009
- ⟨1041⟩ Biologics . . . 2011
- ⟨1045⟩ Biotechnology-Derived Articles . . . 2011
- ⟨1048⟩ Quality of Biotechnological Products: Analysis of the Expression Construct in Cells Used for Production of r-DNA Derived Protein Products . . . 2022
- ⟨1049⟩ Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products . . . 2023
- ⟨1050⟩ Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin . . . 2026
- ⟨1051⟩ Cleaning Glass Apparatus . . . 2036
- ⟨1061⟩ Color—Instrumental Measurement . . . 2036
- ⟨1074⟩ Excipient Biological Safety Evaluation Guidelines . . . 2037
- ⟨1078⟩ Principles of Good Manufacturing Practices for Bulk Pharmaceutical Excipients . . . 2040
- ⟨1081⟩ Gel Strength of Gelatin . . . 2049
- ⟨1086⟩ Impurities in Official Articles . . . 2049
- ⟨1088⟩ In Vitro and In Vivo Evaluation of Dosage Forms . . . 2051
- ⟨1090⟩ In Vivo Bioequivalence Guidances . . . 2056
- ⟨1091⟩ Labeling of Inactive Ingredients . . . 2098
- ⟨1101⟩ Medicine Dropper . . . 2099
- ⟨1111⟩ Microbiological Attributes of Nonsterile Pharmaceutical Products . . . 2099
- ⟨1116⟩ Microbiological Evaluation of Clean Rooms and Other Controlled Environments . . . 2099
- ⟨1121⟩ Nomenclature . . . 2106
- ⟨1151⟩ Pharmaceutical Dosage Forms . . . 2107
- ⟨1161⟩ Pharmacy Compounding Practices . . . 2118
- ⟨1171⟩ Phase-Solubility Analysis . . . 2122
- ⟨1176⟩ Prescription Balances and Volumetric Apparatus . . . 2124
- ⟨1181⟩ Scanning Electron Microscopy . . . 2125
- ⟨1191⟩ Stability Considerations in Dispensing Practice . . . 2128
- ⟨1206⟩ Sterile Drug Products for Home Use . . . 2130
- ⟨1211⟩ Sterilization and Sterility Assurance of Compendial Articles . . . 2143
- ⟨1216⟩ Tablet Friability . . . 2148
- ⟨1221⟩ Teaspoon . . . 2149
- ⟨1225⟩ Validation of Compendial Methods . . . 2149
- ⟨1227⟩ Validation of Microbial Recovery from Pharmacopeial Articles . . . 2152
- ⟨1231⟩ Water for Pharmaceutical Purposes . . . 2154
- ⟨1241⟩ Water-Solid Interactions in Pharmaceutical Systems . . . 2163

Admissions

Articles Admitted to *USP 23* by Supplement

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Albendazole Oral Suspension
Allyl Isothiocyanate
Aluminum Chlorohydrate Propylene Glycol
Aminohippuric Acid
Amoxicillin Boluses
Aurothioglucose
Sterile Aurothioglucose Suspension
Barium Sulfate Suspension
Bismuth Subcarbonate
Buspirone Hydrochloride Tablets
Capsicum Oleoresin
Chlorotrianisene
Chlorotrianisene Capsules
Desflurane
Desoxycorticosterone Pivalate
Desoxycorticosterone Pivalate Injectable Suspension
Dioxybenzone
Dioxybenzone and Oxybenzone Cream
Erythromycin Intramammary Infusion
Erythromycin Injection
Flecainide Acetate
Flecainide Acetate Tablets
Glipizide Tablets
Guanethidine Monosulfate
Guanethidine Monosulfate Tablets
Ketorolac Tromethamine
Ketorolac Tromethamine Injection
Ketorolac Tromethamine Tablets
Mepenzolate Bromide
Mepenzolate Bromide Tablets
Methenamine Hippurate
Methenamine Hippurate Tablets
Metoprolol Fumarate
Monensin
Monensin Granulated
Monensin Premix
Monensin Sodium
Nicotine Polacrilex
Nicotine Polacrilex Gum

Oxytocin
Sulfaquinoxaline
Technetium Tc 99m Mebrofenin Injection
Tilmicosin
Tilmicosin Injection
Tolazoline Hydrochloride
Tolazoline Hydrochloride Injection
Troleandomycin
Troleandomycin Capsules
Vancomycin
Vancomycin Injection
Vasopressin

USP Nutritional Supplements

Calcium with Vitamin D Tablets

Second Supplement (May 15, 1995)

USP MONOGRAPHS

Amitraz
Amitraz Concentrate for Dip
Capsicum
Carboplatin
Carboplatin for Injection
Cefmetazole
Cefmetazole Injection
Clobetazole Propionate
Clobetazole Propionate Cream
Clobetazole Propionate Ointment
Clobetazole Propionate Topical Solution
Clotrimazole Lozenges
Flutamide
Flutamide Capsules
Isophane Insulin Human Suspension
Insulin Human Zinc Suspension
Extended Insulin Human Zinc Suspension
Iobenguane I 123 Injection
Mebendazole Oral Suspension
Mometasone Furoate
Mometasone Furoate Cream
Mometasone Furoate Ointment
Mometasone Furoate Topical Solution
Pancrelipase Delayed-Release Capsules
Penicillin G, Neomycin, Polymyxin B, Hydrocortisone Acetate, and
Hydrocortisone Succinate Topical Suspension
Phensuximide

Phensuximide Capsules
Phenylpropanolamine Bitartrate
Potassium Nitrate
Potassium Nitrate Solution
Rifabutin
Rifabutin Capsules
Sodium Fluoride and Acidulated Phosphate Topical Solution
Strontium Chloride Sr 89 Injection
Technetium Tc 99m Exametazime Injection
Technetium Tc 99m Sestamibi Injection
Ursodiol
Ursodiol Capsules

USP Nutritional Supplements

Oil- and Water-Soluble Vitamins Oral Solution
Oil- and Water-Soluble Vitamins with Minerals Oral Solution
Water-Soluble Vitamins with Minerals Oral Solution

Third Supplement (November 15, 1995)

USP MONOGRAPHS

Acebutolol Hydrochloride
Arsanilic Acid
Benzocaine Gel
Benzocaine and Menthol Topical Acrosol
Bretylium Tosylate
Bretylium Tosylate Injection
Bretylium Tosylate in Dextrose Injection
Buprenorphine Hydrochloride
Captopril and Hydrochlorothiazide Tablets
Methionine C 11 Injection
Sodium Acetate C 11 Injection
Carteolol Hydrochloride
Carteolol Hydrochloride Ophthalmic Solution
Carteolol Hydrochloride Tablets
Cefotetan
Cefotetan Injection
Elm
Ergoloid Mesylates Capsules
Flunixin Meglumine
Flunixin Meglumine Granules
Flunixin Meglumine Injection
Flunixin Meglumine Paste
Gentamicin Sulfate and Betamethasone Acetate Ophthalmic Solution
Gentamicin Sulfate and Betamethasone Valerate Ointment
Gentamicin Sulfate and Betamethasone Valerate Otic Solution

Gentamicin Sulfate and Betamethasone Valerate Topical Solution
Guaifenesin and Pseudoephedrine Hydrochloride Capsules
Guaifenesin, Pseudoephedrine Hydrochloride, and Dextromethorphan Hydrobromide Capsules
Ibuprofen Oral Suspension
Ibuprofen and Pseudoephedrine Hydrochloride Tablets
Indium In 111 Chloride Solution
Metacresol
Omeprazole
Selegiline Hydrochloride
Selegiline Hydrochloride Tablets
Simvastatin
Technetium Tc 99m Mertiatide Injection
Technetium Tc 99m Red Blood Cells Injection

Fourth Supplement (May 15, 1996)

USP MONOGRAPHS

Aspirin Boluses
Atenolol
Atenolol Injection
Atenolol Tablets
Atenolol and Chlorthalidone Tablets
Azithromycin for Oral Suspension
Benzocaine Lozenges
Cephapirin Benzathine
Cephapirin Benzathine Intramammary Infusion
Cephapirin Sodium Intramammary Infusion
Chlorophyllin Copper Complex Sodium
Clindamycin Phosphate Vaginal Cream
Gadopentetate Dimeglumine Injection
Guanfacine Hydrochloride
Guanfacine Tablets
Ioxaglate Meglumine and Ioxaglate Sodium Injection
Ioxaglic Acid
Ketoprofen
Neomycin Boluses
Ofloxacin
Penbutolol Sulfate
Penbutolol Sulfate Tablets
Perflubron
Piperacillin
Pipercillin Sodium
Piperacillin for Injection
Potassium Bitartrate

Fifth Supplement (November 15, 1996)

USP MONOGRAPHS

Aluminum Chlorohydrate Polyethylene Glycol
Aluminum Dichlorohydrate
Aluminum Dichlorohydrate Solution
Aluminum Dichlorohydrate Polyethylene Glycol
Aluminum Dichlorohydrate Propylene Glycol
Aluminum Sesquichlorohydrate
Aluminum Sesquichlorohydrate Solution
Aluminum Sesquichlorohydrate Polyethylene Glycol
Aluminum Sesquichlorohydrate Propylene Glycol
Aluminum Sulfate and Calcium Acetate Tablets for Topical Solution
Aluminum Zirconium Octachlorohydrate Solution
Aluminum Zirconium Octachlorohydrate Gly Solution
Aluminum Zirconium Pentachlorohydrate Solution
Aluminum Zirconium Pentachlorohydrate Gly Solution
Aluminum Zirconium Tetrachlorohydrate Solution
Aluminum Zirconium Tetrachlorohydrate Gly Solution
Aluminum Zirconium Trichlorohydrate Solution
Aluminum Zirconium Trichlorohydrate Gly Solution
Amrinone
Amrinone Injection
Biological Indicator for Steam Sterilization, Self-Contained
Calcium Carbonate Lozenges
Dobutamine Injection
Nicotine
Nicotine Transdermal System
Oxytriphyline Tablets
Verapamil Hydrochloride Extended-Release Tablets
Sterile Purified Water

Sixth Supplement (May 15, 1997)

USP MONOGRAPHS

Amdinocillin
Amdinocillin for Injection
Amoxicillin for Injectable Suspension
Ampicillin for Injection
Ampicillin Injectable Oil Suspension
Ampicillin for Injectable Suspension
Ampicillin Sodium
Ampicillin and Sulbactam for Injection
Azlocillin Sodium
Azlocillin for Injection

Betamethasone Sodium Phosphate and Betamethasone Acetate Injectable Suspension
Bismuth Subsalicylate
Capsaicin
Raclopride C 11 Injection
Cefotetan for Injection
Cefotetan Disodium
Clindamycin Injection
Clindamycin for Injection
Corticotropin Zinc Hydroxide Injectable Suspension
Cortisone Acetate Injectable Suspension
Dexamethasone Acetate Injectable Suspension
Diclofenac Sodium
Diclofenac Sodium Delayed-Release Tablets
Epinephrine Injectable Oil Suspension
Estradiol Injectable Suspension
Estrone Injectable Suspension
Glyburide Tablets
Hydrocortisone Injectable Suspension
Hydrocortisone Acetate Injectable Suspension
Indium In 111 Pentetreotide Injection
Ioversol
Ioversol Injection
Levmetamfetamine
Magnesium Citrate
Magnesium Sulfate in Dextrose Injection
Medroxyprogesterone Acetate Injectable Suspension
Methylprednisolone Acetate Injectable Suspension
Penicillin G Benzathine Injectable Suspension
Penicillin G Benzathine and Pencillin G Procaine Injectable Suspension
Penicillin G Procaine
Penicillin G Procaine Injectable Suspension
Penicillin G Procaine for Injectable Suspension
Pencillin G Procaine with Aluminum Stearate Injectable Oil Suspension
Penicillin G Procaine and Dihydrostreptomycin Sulfate Injectable Suspension
Penicillin G Procaine, Dihydrostreptomycin Sulfate, Chlorpheniramine Maleate, and
Dexamethasone Injectable Suspension
Penicillin G Procaine, Dihydrostreptomycin Sulfate, and Prednisolone Injectable
Suspension
Phenylbutazone Boluses
Phenylbutazone Injection Prednisolone Acetate Injectable Suspension
Prednisolone Tebutate Injectable Suspension
Progesterone Injectable Suspension
Propylidone Injectable Oil Suspension
Spectinomycin for Injectable Suspension
Sulbactam Sodium
Testosterone Injectable Suspension

Triamcinolone Acetonide Injectable Suspension
Triamcinolone Diacetate Injectable Suspension
Triamcinolone Hexacetonide Injectable Suspension

Seventh Supplement (November 15, 1997)

USP MONOGRAPHS

Acetazolamide for Injection
Amobarbital Sodium for Injection
Bleomycin Sulfate
Bleomycin for Injection
Capreomycin Sulfate
Capreomycin for Injection
Carbenicillin Disodium
Carbenicillin for Injection
Mespiperone C 11 injection
Cefazolin Sodium
Cefazolin Injection
Cefazolin for Injection
Ceforanide
Chlordiazepoxide Hydrochloride for Injection
Clorazepate Dipotassium Tablets
Deferoxamine Mesylate for Injection
Ethopabate
Etoposide Injection
Fluoxetine Hydrochloride
Fluoxetine Capsules
Gentamicin Uterine Infusion
Iobenguane I 131 Injection
Mandelic Acid
Mesalamine
Mesalamine Extended-Release Capsules
Mesalamine Rectal Suspension
Pamabrom
Pheniramine Maleate
Prednisone Injectable Suspension
Streptomycin Sulfate
Streptomycin Injection
Streptomycin for Injection
Technetium Tc 99m Bicisate Injection
Thiacetarsamide
Thiacetarsamide Sodium Injection
Vinblastine Sulfate for Injection
Zalcitabine
Zalcitabine Tablets

Eighth Supplement (May 15, 1998)

USP MONOGRAPHS

Acyclovir Ointment
Alfentanil Hydrochloride
Alfenatanil Injection
Bacitracin for Injection
Bisacodyl Rectal Suspension
Calcium Acetate Tablets
Cefamandole Nafate
Cefmenoxime Hydrochloride
Cefonicid Sodium
Cefonicid for Injection
Cefoperazone Injection
Cefoperazone for Injection
Cefotaxime for Injection
Cefotiam Hydrochloride
Ceftizoxime Injection
Ceftizoxime for Injection
Ceftriaxone Injection
Ceftriaxone for Injection
Cefuroxime Injection
Cefuroxime for Injection
Cephalothin Injection
Cephalothin for Injection
Cephapirin Sodium
Cephapirin for Injection
Clarithromycin for Oral Suspension
Dimethyl Sulfoxide Gel
Dimethyl Sulfoxide Topical Solution
Doxycycline for Injection
Enalapril Maleate and Hydrochlorothiazide Tablets
Eucalyptol
Guaifenesin for Injection
Indium In 111 Satumomab Pendetide Injection
Isradipine
Lactase
Menthol Lozenges
Moricizine Hydrochloride
Moricizine Hydrochloride Tablets
Naftifine Hydrochloride
Naftifine Hydrochloride Cream
Naftifine Hydrochloride Gel
Neomycin for Injection
Poloxalene
Polymyxin B for Injection

Quazepam
Quazepam Tablets
Sargramostim
Sargramostim for Injection
Sulfaquinoxaline Oral Solution
Trenbolone Acetate
Trifluridine
Tylosin
Tylosin Granulated
Zidovudine
Zidovudine Capsules
Zidovudine Injection
Zidovudine Oral Solution

Ninth Supplement (November 15, 1998)

USP MONOGRAPHS

Capsules Containing at Least Three of the Following—Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine
Oral Solution Containing at Least Three of the Following—Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Phenylpropanolamine
Capsules Containing at Least Three of the Following—Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine
Oral Powder Containing at Least Three of the Following—Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine
Oral Solution Containing at Least Three of the Following—Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine
Tablets Containing at Least Three of the Following—Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine
Acetaminophen, Dextromethorphan Hydrobromide, Doxylamine Succinate, and Pseudoephedrine Hydrochloride Oral Solution
Acetaminophen, Diphenhydramine Hydrochloride, and Pseudoephedrine Hydrochloride Tablets
Acyclovir Capsules
Acyclovir for Injection
Acyclovir Oral Suspension
Acyclovir Tablets
Albendazole Tablets
Altretamine
Altermine Capsules
Astemizole
Astemizole Tablets
Calcium and Magnesium Carbonates Oral Suspension
Chloramphenicol Sodium Succinate
Chloramphenicol Sodium Succinate for Injection
Chlorpheniramine Maleate and Pseudoephedrine Hydrochloride Oral Solution

Cholecalciferol Solution
Clindamycin Injection
Clindamycin for Injection
Cocaine and Tetracaine Hydrochlorides and Epinephrine Topical Solution
Colistimethate Sodium
Colistimethate for Injection
Cytarabine for Injection
Dexbrompheniramine Maleate and Pseudoephedrine Sulfate Oral Solution
Dihydrostreptomycin Injection
Dihydroxyacetone
Floaxuridine for Injection
Gentamicin Injection
Hydralazine Hydrochloride Oral Solution
Ifosfamide for Injection
Indocyanine Green for Injection
Indomethacin for Injection
Ioxilan
Ioxilan Injection
Kanamycin Injection
Levocarnitine Injection
Lincomycin Injection
Magnesium Carbonate and Citric Acid for Oral Solution
Magnesium Citrate for Oral Solution
Methicillin Sodium
Methicillin for Injection
Mezlocillin Sodium
Mezlocillin for Injection
Minocycline for Injection
Minoxidil Topical Solution
Naltrexone Hydrochloride
Naltrexone Hydrochloride Tablets
Narasin Granular
Narasin Premix
Oxacillin Injection
Oxacillin for Injection
Oxytetracycline for Injection
Penicillin G Sodium
Phenylpropanolamine Hydrochloride Capsules
Phenylpropanolamine Hydrochloride Oral Solution
Phenylpropanolamine Hydrochloride Tablets
Pseudoephedrine Hydrochloride Extended-Release Tablets
Rifampin Oral Suspension
Rimexolone
Rimexolone Ophthalmic Suspension
Roxarsone
Selenomethionine

Simvastatin Tablets
Sodium Hypochlorite Topical Solution
Succinylcholine Chloride for Injection
Technetium Tc 99m Tetrofosmin Injection
Tetracaine Hydrochloride for Injection
Tiletamine Hydrochloride
Tiletamine and Zolazepam for Injection
Tolbutamide for Injection
Triclosan
Urea for Injection
Zolazepam Hydrochloride

Tenth Supplement (May 15, 1999)

USP MONOGRAPHS

Tables Containing at Least Three of the Following—Acetaminophen and Salts of
Chlorpheniramine, Dextromethorphan, and Phenylpropanolamine

Adenosine
Adenosine Injection
Aminophylline Delayed-Release Tablets
Avobenzone
Barium Sulfate Tablets
Bisacodyl Delayed-Release Tablets
Flumazenil C 11 Injection
Cefmetazole Sodium
Cefmetazole for Injection
Cimetidine Hydrochloride
Cimetidine Injection
Cimetidine in Sodium Chloride Injection
Clindamycin Hydrochloride Oral Solution
Cyclosporine Injection
Dexamethasone Oral Solution
Dextran 40
Dextran 40 in Dextrose Injection
Dextran 40 in Sodium Chloride Injection
Dextran 70
Dextran 70 in Dextrose Injection
Dextran 70 in Sodium Chloride Injection
Dirithromycin
Dirithromycin Delayed-Release Tablets
Etodolac
Etodolac Tablets
Gonadorelin Hydrochloride
Gonadorelin for Injection
Homosalate
Indium In 111 Capromab Pendetide Injection

Iopromide
Isoamyl Methoxycinnamate
Isotretinoin Capsules
Lincomycin Hydrochloride Soluble Powder
Menthyl Anthranilate
Methenamine Mandelate Delayed-Release Tablets
Methyl Benzylidene Camphor
Mibolerone
Mibolerone Oral Solution
Mitoxantrone Injection
Nafcillin Injection
Nafcillin for Injection
Norfloxacin Ophthalmic Solution
Octocrylene
Octyl Methoxycinnamate
Octyl Salicylate
Ofloxacin Ophthalmic Solution
Ondansetron Hydrochloride
Ondansetron Injection
Oxfendazole
Oxfendazole Oral Suspension
Oxytetracycline Hydrochloride Soluble Powder
Phenobarbital Sodium for Injection
Phenylbenzimidazole Sulfonic Acid
Potassium Iodide Delayed-Release Tablets
Potassium Perchlorate
Potassium Perchlorate Capsules
Pralidoxime Chloride for Injection
Secobarbital Sodium for Injection
Sincalide for Injection
Sodium Nitroprusside for Injection
Streptomycin Sulfate
Streptomycin Injection
Streptomycin for Injection
Sulfamethoxazole and Trimethoprim Injection
Sulfasalazine Delayed-Release Tablets
Sulisobenzone
Ticarcillin Disodium
Ticarcillin for Injection
Ticarcillin and Clavulanic Acid Injection
Ticarcillin and Clavulanic Acid for Injection
Tobramycin Injection
Tobramycin for Injection
Trimethoprim Sulfate
Trolamine Salicylate
Vidarabine

Wheat Bran
 Xylazine
 Xylazine Hydrochloride
 Xylazine Injection

Official Titles Changed by Supplement

Parenthetical notation following the title indicates the Supplement in which the title change became official in USP 23.

Current Title	Former Title
Acetazolamide for Injection (7S)	Sterile Acetazolamide Sodium
Amdinocillin (6S)	Sterile Amdinocillin
Amdinocillin for Injection (6S)	Sterile Amdinocillin
Amobarbital Sodium (7S)	Sterile Amobarbital Sodium
Amobarbital Sodium for Injection (7S)	Sterile Amobarbital Sodium
Amoxicillin (6S)	Sterile Amoxicillin
Amoxicillin for Injectable Suspension (6S)	Sterile Amoxicillin for Suspension
Ampicillin (6S)	Sterile Ampicillin
Ampicillin for Injection (6S)	Sterile Ampicillin
Ampicillin Injectable Oil Suspension (6S)	Sterile Ampicillin Suspension
Ampicillin for Injectable Suspension (6S)	Sterile Ampicillin for Suspension
Ampicillin Sodium (6S)	Sterile Ampicillin Sodium
Ampicillin and Sulbactam for Injection (6S)	Sterile Ampicillin Sodium and Sulbactam Sodium
Aurothioglucose Injectable Suspension (7S)	Sterile Aurothioglucose Suspension
Azlocillin Sodium (6S)	Sterile Azlocillin Sodium
Azlocillin for Injection (6S)	Sterile Azlocillin Sodium
Aztreonam (7S)	Sterile Aztreonam
Aztreonam for Injection (7S)	Sterile Aztreonam
Betamethasone Sodium Phosphate and Betamethasone Acetate Injectable Suspension (6S)	Sterile Betamethasone Sodium Phosphate and Betamethasone Acetate Suspension
Bisacodyl Delayed-Release Tablets (10S)	Bisacodyl Tablets
Bleomycin Sulfate (7S)	Sterile Bleomycin Sulfate
Belomycin for Injection (7S)	Sterile Bleomycin Sulfate
Bupivacaine Hydrochloride in Dextrose Injection (2S)	Bupivacaine in Dextrose Injection
Bupivacaine Hydrochloride and Epinephrine Injection (2S)	Bupivacaine and Epinephrine Injection
Capreomycin Sulfate (7S)	Sterile Capreomycin Sulfate
Capreomycin for Injection (7S)	Sterile Capreomycin Sulfate
Carbenicillin Disodium (7S)	Sterile Carbenicillin Disodium

Current Title	Former Title
Carbenicillin for Injection (7S)	Sterile Carbenicillin Disodium
Cefazolin Sodium (7S)	Sterile Cefazolin Sodium
Cefazolin Injection (7S)	Cefazolin Sodium Injection
Cefazolin for Injection (7S)	Sterile Cefazolin Sodium
Cefmenoxime Hydrochloride (8S)	Sterile Cefmenoxime Hydrochloride
Cefmetazole Sodium (10S)	Sterile Cefmetazole Sodium
Cefmetazole for Injection (10S)	Sterile Cefmetazole Sodium
Cefonicid Sodium (8S)	Sterile Cefonicid Sodium
Cefonicid for Injection (8S)	Sterile Cefonicid Sodium
Cefoperazone Sodium (8S)	Sterile Cefoperazone Sodium
Cefoperazone Injection (8S)	Cefoperazone Sodium Injection
Cefoperazone for Injection (8S)	Sterile Cefoperazone Sodium
Ceforanide (7S)	Sterile Ceforanide
Ceforanide for Injection (7S)	Sterile Ceforanide
Cefotaxime Sodium (8S)	Sterile Cefotaxime Sodium
Cefotaxime Injection (8S)	Cefotaxime Sodium Injection
Cefotaxime for Injection (8S)	Sterile Cefotaxime Sodium
Cefotetan for Injection (6S)	Sterile Cefotetan Disodium
Cefotetan Disodium (6S)	Sterile Cefotetan Disodium
Cefotiam Hydrochloride (8S)	Sterile Cefotiam Hydrochloride
Cefotiam for Injection (8S)	Sterile Cefotiam Hydrochloride
Cefoxitin Injection (1S)	Cefoxitin Sodium Injection
Cefoxitin for Injection (1S)	Sterile Cefoxitin Sodium
Ceftizoxime Sodium (8S)	Sterile Ceftizoxime Sodium
Ceftizoxime Injection (8S)	Ceftizoxime Sodium Injection
Ceftizoxime for Injection (8S)	Sterile Ceftizoxime Sodium
Ceftriaxone Sodium (8S)	Sterile Ceftriaxone Sodium
Ceftriaxone Injection (8S)	Ceftriaxone Sodium Injection
Ceftriaxone for Injection (8S)	Sterile Ceftriaxone Sodium
Cefuroxime Sodium (8S)	Sterile Cefuroxime Sodium
Cefuroxime Injection (8S)	Cefuroxime Sodium Injection
Cefuroxime for Injection (8S)	Sterile Cefuroxime Sodium
Cephalothin Injection (8S)	Cephalothin Sodium Injection
Cephalothin for Injection (8S)	Cephalothin Sodium for Injection
Cephapirin Sodium (8S)	Sterile Cephapirin Sodium
Cephapirin for Injection (8S)	Sterile Cephapirin Sodium
Cephalothin Sodium (8S)	Sterile Cephalothin Sodium
Cephradine (8S)	Sterile Cephradine
Cephradine for Injection (8S)	Sterile Cephradine
Chlordiazepoxide Hydrochloride (7S)	Sterile Chlordiazepoxide Hydrochloride
Chlordiazepoxide Hydrochloride for Injection (7S)	Sterile Chlordiazepoxide Hydrochloride
Cilastatin Sodium (1S)	Sterile Cilastatin Sodium
Clavulanate Potassium (10S)	Sterile Clavulanate Potassium

Current Title	Former Title
Clindamycin Phosphate (9S)	Sterile Clindamycin Phosphate
Clindamycin Injection (9S)	Clindamycin Phosphate Injection
Clindamycin for Injection (9S)	Sterile Clindamycin Phosphate
Colistimethate Sodium (9S)	Sterile Colistimethate Sodium
Colistimethate for Injection (9S)	Sterile Colistimethate Sodium
Corticotropin Zinc Hydroxide Injectable Suspension (6S)	Sterile Corticotropin Zinc Hydroxide Suspension
Cortisone Acetate Injectable Suspension (6S)	Sterile Cortisone Acetate Suspension
Cromolyn Sodium Inhalation Solution (1S)	Cromolyn Sodium Inhalation
Cyclosporine Injection (10S)	Cyclosporine Concentrate for Injection
Cytarabine (9S)	Sterile Cytarabine
Cytarabine for Injection (9S)	Sterile Cytarabine
Deferoxamine Mesylate (7S)	Sterile Deferoxamine Mesylate
Deferoxamine Mesylate for Injection (7S)	Sterile Deferoxamine Mesylate
Dexamethasone Acetate Injectable Suspension (6S)	Sterile Dexamethasone Acetate Suspension
Dihydrostreptomycin Sulfate (9S)	Sterile Dihydrostreptomycin Sulfate
Dihydrostreptomycin Injection (9S)	Dihydrostreptomycin Sulfate Injection
Dobutamine for Injection (1S)	Dobutamine Hydrochloride for Injection
Epinephrine Injectable Oil Suspension (6S)	Sterile Epinephrine Oil Suspension
Estradiol Injectable Suspension (6S)	Sterile Estradiol Suspension
Estrone Injectable Suspension (6S)	Sterile Estrone Suspension
Hydrocortisone Injectable Suspension (6S)	Sterile Hydrocortisone Suspension
Hydrocortisone Acetate Injectable Suspension (6S)	Sterile Hydrocortisone Acetate Suspension
Ifosfamide (9S)	Sterile Ifosfamide
Ifosfamide for Injection (9S)	Sterile Ifosfamide
Imipenem (1S)	Sterile Imipenem
Imipenem and Cilastatin for Injection (1S)	Imipenem and Cilastatin Sodium for Injection
Imipenem and Cilastatin for Injectable Suspension (1S)	Sterile Imipenem and Cilastatin Sodium
Indocyanine Green (9S)	Sterile Indocyanine Green
Indocyanine Green for Injection (9S)	Sterile Indocyanine Green
Indomethacin Sodium (9S)	Sterile Indomethacin Sodium
Indomethacin for Injection (9S)	Sterile Indomethacin Sodium
Kanamycin Sulfate (9S)	Sterile Kanamycin Sulfate
Kanamycin Injection (9S)	Kanamycin Sulfate Injection
Lidocaine Hydrochloride and Epinephrine Injection (2S)	Lidocaine and Epinephrine Injection

Current Title	Former Title
Lincomycin Hydrochloride (9S)	Sterile Lincomycin Hydrochloride
Lincomycin Injection (9S)	Lincomycin Hydrochloride Injection
Medroxyprogesterone Acetate Injectable Suspension (6S)	Sterile Medroxyprogesterone Acetate Suspension
Methicillin Sodium (9S)	Sterile Methicillin Sodium
Methicillin for Injection (9S)	Methicillin Sodium for Injection
Methylprednisolone Acetate Injectable Suspension (6S)	Sterile Methylprednisolone Acetate Suspension
Mezlocillin Sodium (9S)	Sterile Mezlocillin Sodium
Mezlocillin for Injection (9S)	Sterile Mezlocillin Sodium
Minocycline Hydrochloride (9S)	Sterile Minocycline Hydrochloride
Minocycline for Injection (9S)	Sterile Minocycline Hydrochloride
Mitoxantrone Injection (10S)	Mitoxantrone for Injection Concentrate
Nafcillin Sodium (10S)	Sterile Nafcillin Sodium
Nafcillin Injection (10S)	Nafcillin Sodium Injection
Nafcillin for Injection (10S)	Nafcillin Sodium for Injection and Sterile Nafcillin Sodium
Oxacillin Sodium (9S)	Sterile Oxacillin Sodium
Oxacillin Injection (9S)	Oxacillin Sodium Injection
Oxacillin for Injection (9S)	Oxacillin Sodium for Injection
Oxytetracycline (9S)	Sterile Oxytetracycline
Oxytetracycline Hydrochloride (9S)	Sterile Oxytetracycline Hydrochloride
Oxytetracycline for Injection (9S)	Oxytetracycline Hydrochloride for Injection
Penicillin G Benzathine (6S)	Sterile Penicillin G Benzathine
Penicillin G Benzathine Injectable Suspension (6S)	Sterile Penicillin G Benzathine Suspension
Penicillin G Benzathine and Penicillin G Procaine Injectable Suspension (6S)	Sterile Penicillin G Benzathine and Penicillin G Procaine Suspension
Penicillin G Potassium (9S)	Sterile Penicillin G Potassium
Penicillin G Potassium for Injection (9S)	Sterile Penicillin G Potassium
Penicillin G Procaine (6S)	Sterile Penicillin G Procaine
Penicillin G Procaine Injectable Suspension (6S)	Sterile Penicillin G Procaine Suspension
Penicillin G Procaine for Injectable Suspension (6S)	Sterile Penicillin G Procaine for Suspension
Penicillin G Procaine with Aluminum Stearate Injectable Oil Suspension (6S)	Sterile Penicillin G Procaine with Aluminum Stearate Suspension
Penicillin G Procaine and Dihydrostreptomycin Sulfate Injectable Suspension (6S)	Sterile Penicillin G Procaine and Dihydrostreptomycin Sulfate Suspension
Penicillin G Procaine, Dihydrostreptomycin Sulfate Chlorpheniramine Maleate, and Dexamethasone Injectable Suspension (6S)	Sterile Penicillin G Procaine, Dihydrostreptomycin Sulfate, Chlorpheniramine Maleate, and Dexamethasone Suspension

Current Title	Former Title
Penicillin G Procaine, Dihydrostreptomycin Sulfate, and Prednisolone Injectable Suspension (6S)	Sterile Penicillin G Procaine, Dihydrostreptomycin Sulfate, and Prednisolone Suspension
Penicillin G Sodium (9S)	Sterile Penicillin G Sodium
Penicillin G Sodium for Injection (9S)	Sterile Penicillin G Sodium
Phenobarbital Sodium (10S)	Sterile Phenobarbital Sodium
Phenobarbital Sodium for Injection (10S)	Sterile Phenobarbital Sodium
Piperacillin Sodium (4S)	Sterile Piperacillin Sodium
Piperacillin for Injection (4S)	Sterile Piperacillin Sodium
Pralidoxime Chloride (10S)	Sterile Pralidoxime Chloride
Pralidoxime Chloride for Injection (10S)	Sterile Pralidoxime Chloride
Prednisolone Acetate Injectable Suspension (6S)	Sterile Prednisolone Acetate Suspension
Prednisolone Tebutate Injectable Suspension (6S)	Sterile Prednisolone Tebutate Suspension
Procaine Hydrochloride (10S)	Sterile Procaine Hydrochloride
Prochlorperazine Oral Solution (3S)	Prochlorperazine Edisylate Syrup
Progesterone Injectable Suspension (6S)	Sterile Progesterone Suspension
Propylidone Injectable Oil Suspension (6S)	Sterile Propylidone Oil Suspension
Secobarbital Sodium (10S)	Sterile Secobarbital Sodium
Secobarbital Sodium for Injection (10S)	Sterile Secobarbital Sodium
Sodium Nitroprusside (10S)	Sterile Sodium Nitroprusside
Sodium Nitroprusside for Injection (10S)	Sterile Sodium Nitroprusside
Spectinomycin Hydrochloride (8S)	Sterile Spectinomycin Hydrochloride
Spectinomycin for Injectable Suspension (6S)	Sterile Spectinomycin Hydrochloride for Suspension
Streptomycin Sulfate (10S)	Sterile Streptomycin Sulfate
Streptomycin Injection (10S)	Streptomycin Sulfate Injection
Streptomycin for Injection (10S)	Sterile Streptomycin Sulfate
Sulfactam Sodium (6S)	Sterile Sulfactam Sodium
Sulfamethoxazole and Trimethoprim Injection (10S)	Sulfamethoxazole and Trimethoprim for Injection Concentrate
Testosterone Injectable Suspension (6S)	Sterile Testosterone Suspension
Ticarcillin Disodium (10S)	Sterile Ticarcillin Disodium
Ticarcillin for Injection (10S)	Sterile Ticarcillin Disodium
Ticarcillin and Clavulanic Acid Injection (10S)	Ticarcillin Disodium and Clavulanate Potassium Injection
Ticarcillin and Clavulanic Acid for Injection (10S)	Sterile Ticarcillin Disodium and Clavulanate Potassium
Tobramycin Sulfate (10S)	Sterile Tobramycin Sulfate
Tobramycin Injection (10S)	Tobramycin Sulfate Injection
Tobramycin for Injection (10S)	Sterile Tobramycin Sulfate
Triamcinolone Acetonide Injectable Suspension (6S)	Sterile Triamcinolone Acetonide Suspension

Current Title	Former Title
Triamcinolone Diacetate Injectable Suspension (6S)	Sterile Triamcinolone Diacetate Suspension
Triamcinolone Hexacetonide Injectable Suspension (6S)	Sterile Triamcinolone Hexacetonide Suspension
Vidarabine (10S)	Sterile Vidarabine
Vinblastine Sulfate (7S)	Sterile Vinblastine Sulfate
Vinblastine Sulfate for Injection (7S)	Sterile Vinblastine Sulfate
Sterile Bacteriostatic Water for Injection (5S)	Bacteriostatic Water for Injection

Changes in Official Titles

USP 24 Title	USP 23 Title
Bacitracin	Sterile Bacitracin
Bacitracin for Injection	Sterile Bacitracin
Bacitracin Zinc	Sterile Bacitracin Zinc
Cefamandole Nafate	Sterile Cefamandole Nafate
Cefamandole Nafate for Injection	Sterile Cefamandole Nafate
Ceftazidime	Sterile Ceftazidime
Chloramphenicol	Sterile Chloramphenicol
Chloramphenicol Sodium Succinate	Sterile Chloramphenicol Sodium Succinate
Chloramphenicol Sodium Succinate for Injection	Sterile Chloramphenicol Sodium Succinate
Chlortetracycline Hydrochloride	Sterile Chlortetracycline Hydrochloride
Cloxacillin Benzathine	Sterile Cloxacillin Benzathine
Cloxacillin Sodium	Sterile Cloxacillin Sodium
Doxycycline Hyclate	Sterile Doxycycline Hyclate
Doxycycline for Injection	Doxycycline Hyclate for Injection
Floxuridine	Sterile Floxuridine
Floxuridine for Injection	Sterile Floxuridine
Gentamicin Sulfate	Sterile Gentamicin Sulfate
Gentamicin Injection	Gentamicin Sulfate Injection
Lidocaine Hydrochloride	Sterile Lidocaine Hydrochloride
Neomycin Sulfate	Sterile Neomycin Sulfate
Neomycin for Injection	Sterile Neomycin Sulfate
Polymyxin B Sulfate	Sterile Polymyxin B Sulfate
Polymyxin B For Injection	Sterile Polymyxin B Sulfate
Succinylcholine Chloride	Sterile Succinylcholine Chloride
Succinylcholine Chloride for Injection	Sterile Succinylcholine Chloride
Tetracaine Hydrochloride	Sterile Tetracaine Hydrochloride
Tetracaine Hydrochloride for Injection	Sterile Tetracaine Hydrochloride
Tetracycline Hydrochloride	Sterile Tetracycline Hydrochloride
Tetracycline Hydrochloride for Injection	Sterile Tetracycline Hydrochloride

<i>USP 24 Title</i>	<i>USP 23 Title</i>
Tolbutamide	Sterile Tolbutamide Sodium
Tolbutamide for Injection	Sterile Tolbutamide Sodium
Urea	Sterile Urea
Urea for Injection	Sterile Urea

Revisions Appearing in *USP 24* That Were Not Included in *USP 23* Including Supplements

- ⟨467⟩ Organic Volatile Impurities
- ⟨1074⟩ Excipient Biological Safety Evaluation Guidelines (new)
- ⟨1078⟩ Principles of Good Manufacturing Practices for Bulk Pharmaceutical Excipients (new)

Articles Included in *USP 23* but Not Included in *USP 24*

Acetaminophen, Aspirin, and Caffeine Capsules
 Acetaminophen and Caffeine Capsules
 Amdinocillin
 Amdinocillin for Injection
 Aminobenzoate Potassium
 Aminobenzoate Potassium Capsules
 Aminobenzoate Potassium for Oral Solution
 Aminobenzoate Potassium Tablets
 Aminobenzoate Sodium
 Ampicillin Injectable Oil Suspension
 Ampicillin Tablets
 Ampicillin and Probenecid Capsules
 Aspirin, Codeine Phosphate, and Caffeine Capsules
 Aspirin, Codeine Phosphate, and Caffeine Tablets
 Azlocillin Sodium
 Azlocillin for Injection
 Benzthiazide
 Benzthiazide Tablets
 Bromodiphenhydramine Hydrochloride Capsules
 Butabarbital Sodium Capsules
 Candididin
 Candididin Ointment
 Candididin Vaginal Tablets
 Carboprost Tromethamine
 Carboprost Tromethamine Injection
 Cefamandole Sodium for Injection
 Sterile Cefamandole Sodium
 Chlorotrianisene
 Chlorotrianisene Capsules
 Chlorprothixene

Chlorprothixene Injection
Chlorprothixene Oral Suspension
Chlorprothixene Tablets
Chlortetracycline Hydrochloride Capsules
Clidinium Bromide Capsules
Cyclacillin
Cyclacillin for Oral Suspension
Cyclacillin Tablets
Cyclizine
Cyclizine Lactate Injection
Demeclocycline Hydrochloride and Nystatin Capsules
Demeclocycline Hydrochloride and Nystatin Tablets
Desipramine Hydrochloride Capsules
Dihydroxyaluminum Aminoacetate Capsules
Dihydroxyaluminum Aminoacetate Tablets
Dinoprost Tromethamine
Dinoprost Tromethamine Injection
Dyphylline and Guaifenesin Tablets
Ephedrine Sulfate Tablets
Ephedrine Sulfate and Phenobarbital Capsules
Epinephrine Injectable Oil Suspension
Diluted Erythryl Tetranitrate
Erythryl Tetranitrate Tablets
Sterile Erythromycin Gluceptate
Ethopropazine Hydrochloride
Ethopropazine Hydrochloride Tablets
Flurandrenolide Cream
Flurandrenolide Ointment
Glutethimide
Glutethimide Capsules
Glutethimide Tablets
Haloprogin
Haloprogin Cream
Haloprogin Topical Solution
Hetacillin Potassium
Hetacillin Potassium Intramammary Infusion
Hetacillin Potassium Oral Suspension
Hetacillin Potassium Tablets
Hydroxypropyl Methylcellulose 2208
Hydroxypropyl Methylcellulose 2906
Hydroxypropyl Methylcellulose 2910
Iocetamic Acid
Iocetamid Acid Tablets
Ipodate Calcium
Ipodate Calcium for Oral Suspension
Isocarboxazid

Isocarboxazid Tablets
Mepenzolate Bromide
Mepenzolate Bromide Tablets
Mephentermine Sulfate
Mephentermine Sulfate Injection
Mephenytoin
Mephenytoin Tablets
Mephobarbital
Mephobarbital Tablets
Ammoniated Mercury Ointment
Ammoniated Mercury Ophthalmic Ointment
Methdilazine
Methdilazine Tablets
Methenamine and Monobasic Sodium Phosphate Tablets
Metocurine Iodide
Metocurine Iodide Injection
Monobenzene
Monobenzene Cream
Moxalactam Disodium for Injection
Nitrofurazone Cream
Novobiocin Sodium Capsules
Oxamniquine
Oxamniquine Capsules
Oxyphenbutazone
Oxyphenbutazone Tablets
Oxytetracycline and Phenazopyridine Hydrochlorides and Sulfamethizole Capsules
Pancreatin Capsules
Penicillin G Potassium Capsules
Penicillin G Potassium Tablets for Oral Solution
Penicillin G Procaine with Aluminum Stearate Injectable Oil Suspension
Diluted Pentaerythritol Tetranitrate
Pentaerythritol Tetranitrate Tablets
Pentazocine Hydrochloride Tablets
Phenacetamide
Phenacetamide Tablets
Phenolphthalein
Phenolphthalein Tablets
Yellow Phenolphthalein
Phenylbutazone Capsules
Posterior Pituitary Injection
Polythiazide
Polythiazide Tablets
Pralidoxime Chloride Tablets
Prazepam
Prazepam Capsules
Prazepam Tablets

Procaine and Phenylephrine Hydrochlorides Injection
Sterile Propantheline Bromide
Sulfamerazine
Sulfamerazine Tablets
Sulfisoxazole Diolamine
Sulfisoxazole Diolamine Injection
Sulfisoxazole Diolamine Ophthalmic Ointment
Sulfisoxazole Diolamine Ophthalmic Solution
Sutilains
Sutilains Ointment
Terfenadine
Terfenadine Tablets
Terpin Hydrate and Dextromethorphan Hydrobromide Elixir
Tetracycline Phosphate Complex
Tetracycline Phosphate Complex Capsules
Tetracycline Phosphate Complex for Injection
Sterile Tetracycline Phosphate Complex
Tetracycline Phosphate Complex and Novobiocin Sodium Capsules
Thiamylal
Thiamylal Sodium for Injection
Thiethylperazine Malate
Thiethylperazine Malate Injection
Tioconazole Cream
Trimethadione
Trimethadione Capsules
Trimethadione Oral Solution
Trimethadione Tablets
Trimethaphan Camsylate
Trimethaphan Camsylate Injection
Tripelennamine Citrate
Tripelennamine Citrate Elixir
Tyropanoate Sodium
Tyropanoate Sodium Capsules
Vidarabine Concentrate for Injection

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